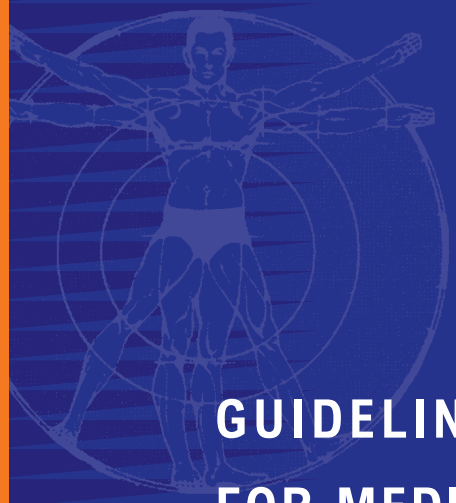

GUIDELINES ON ETHICS FOR MEDICAL RESEARCH:

USE OF ANIMALS IN RESEARCH AND TRAINING

Guidelines on Ethics for Medical Research

Book 3: Use of Animals in Research and Training

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Foreword to the first edition

The use of laboratory animals for research, teaching and the testing of medicines, medical appliances and consumer products is a controversial and difficult issue in modern society.

In 1987 Jenny Remfrey[1] of the Universities Federation for Animal Welfare wrote: "These days, scientists are subject to abuse and attacks from groups of protesters who accuse them of cruel exploitation" and questioned further "Are these attacks based on matters of fact or on questions of attitudes and ethical judgements? How seriously should scientists take them? How should they respond?"

All of these issues are challenging to science and scientists. They pose questions such as the following: Is the welfare of laboratory animals being neglected? Is it being ignored? Are our scientists committing the sins of which they are being accused?

Since the mid-1970s emerging local debate on these matters and a directive from the Medical Research Council led to the institution of an ethical review process and the formal appointment of Animal Ethics Committees at our universities and research institutions.

The inclusion of notes on animal experimentation in early Ethical Consideration documents published by the Medical Research Council in 1979,[2] and in subsequent revisions of this document in 1987[3] and 1993,[4] have served to sensitise biomedical scientists to the interests and welfare of animals used for research.

In 1990 the first National Code for Animal Use in Research, Education, Diagnosis and Testing of Drugs and Related Substances was promulgated by the Minister of Agriculture, Mr Jacob de Villiers, to promote the rational and humane use of laboratory animals and to establish a uniform system of internal control in scientific institutions, and to mandate that 'Animal Ethics Committees' shall control the use and care of experimental animals in research institutions.

The above Code is soon to be superseded by a new revised Code of Practice. This is currently being drafted by a task group appointed by the Standards Division of the South African Bureau of Standards to set standards and practices in animal experimentation that comply with current international norms. It should be consulted as a reference standard which encompasses all aspects of the care and use of laboratory animals. It also

specifies the responsibilities of investigators, institutions and their Ethics Committees in managing animal-based teaching and research.

The role of institutional Animal Ethics Committees is to provide support to investigators in promoting laboratory animal welfare and to help them resolve ethical issues which may arise from their animal studies.

It is also to promote the use of ethical analysis, to increase awareness of the interests of laboratory animals and their welfare needs, to develop initiatives which will lead to the widest application of the 'three R' principles of Humane Experimental Technique, of Russell and Burch,[6] namely replacement, reduction and refinement, and to ensure that the use of animals in an experiment is justified by the relevance of the problems being studied and the likelihood of successful outcomes.

There is also the challenge posed by the philosophical concept of Animal Rights and the influence it exerts in shaping public opinion. This concept needs to be understood and respected since it is aligned towards ending man's inhumanity towards animals in general and irrational and unproductive animal experimentation.

Finally, the educational role of Animal Ethics Committees should serve to establish educational programmes for both animal users and the general public. This is to ensure that the former can appreciate the responsibility and imperatives concerned with animal experimentation, and the latter can be informed why and how animals are used in science and how this can be justified.

It is hoped that these guidelines will contribute to the conduct of animal research in a positive way.

Prof William Pick
MRC Interim President

There are five books in the series *Guidelines on Ethics for Medical Research.*

Book 1

Guidelines on Ethics for Medical Research: General Principles.

Book 2

Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research.

Book 3

Guidelines on Ethics for Medical Research: Use of Animals in Research and Training.

Book 4

Guidelines on Ethics for Medical Research: Use of Biohazards and Radiation.

Book 5

Guidelines on Ethics for Medical Research: HIV Vaccine Trials.

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1. What is the South African Medical Research Council's ethics policy on animal experimentation?

1.1 General policy

1.1.1 The MRC recognises the moral dilemma posed by the use of sentient animals (i.e. animals which can feel sensations and experience emotions) for research, teaching and testing. It subscribes to the ethic of only supporting studies which promise to contribute to the understanding of biology and environmental principles and to the acquisition of knowledge that can reasonably be expected to benefit humans, animals or the environment.

1.1.2 It recognises that all vertebrate animals are protected by law in South Africa (Animals Protection Act No. 71 of 1962) and that it may be an offence in terms of this law to kill or interfere with the well-being of an animal for scientific or educational purposes without justification which is ratified by a formal process of ethical review.

1.1.3 It insists that animals may only be used when the researcher's best efforts to find a non-sentient alternative have been unsuccessful.

1.1.4 It requires optimal standards of animal health and care to be observed to provide good-quality results that enhance credibility and reproducibility.

1.1.5 It requires the 'three R' principles of 'replacement, reduction and refinement' to be adhered to in the planning and conduct of animal studies. These uphold the principles and practice of using the most humane methods on the smallest number of animals that will permit valid scientific information to be acquired.

1.1.6 It accepts that the use of animals in science critically depends on maintaining public confidence in the mechanisms and processes used to ensure that animal experiments are justified and humane.

1.1.7 It recognises that laboratory animals are protected by law in South Africa, and that their use for education, testing and research must be justified.

2. For whom the Guidelines are intended

These guidelines apply to the use of sentient animals for research, teaching and testing within the South African Medical Research Council.

They are applicable to all Medical Research Council (MRC) staff who 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 MRC staff or with financial or other support from the MRC and its employees.

3. Ethical principles

3.1 Moral philosophy

It is accepted that sentient, non-human animals have the capacity to experience a range of physical sensations and emotions and are therefore subjects of moral concern.

3.2 Utilitarian ethic

The use of laboratory animals as research subjects in biomedical science must be justified by the assurance that the potential benefit to either humans, animals and/or the environment, outweighs the potential harm to the animal subjects. Each proposed experiment must therefore be supported by a formal evaluation (an ethical analysis) of harm to animals/benefit to humans, animals or the environment, which will determine that more utility (good) than disutility (harm) will probably result from the proposed experiment - i.e. that the overall likely benefit will outweigh the potential harm to the animals. Furthermore, justification for causing psychological or physical distress, illness or pain to animals should not be based on any explicit or implicit assumption that non-human animals experience these conditions in qualitatively different ways to humans.

3.3 Human obligations towards laboratory animals

Laboratory animals should be able to live, grow, reproduce and interact under conditions and circumstances in which their species' specific needs are met, as far as possible. Special consideration should be given to the needs of social animals in this regard and to animals which have adapted to special circumstances or environments (e.g. nocturnal animals, marine animals, etc.).

3.4 Humaneness and the principles of humane experimental techniques

Experimental procedures which may cause either hunger, thirst, injury, disease, discomfort, fear, distress, deprivation or pain must, by design, keep exposure of animals to these conditions to a minimum. By definition,

humaneness is the practice of reducing the sum total of these conditions experienced by an animal subject to a minimum, or eliminating them altogether, by applying the 'three R' principles of Russell and Burch:[6] replacement, reduction and refinement. The meanings of these principles are as follows:

Replacement of sentient animals with non-sentient research models or systems in order to eliminate the use of animals that can experience unpleasant sensations.

Reduction of the numbers of animals in experiments by design strategies that facilitate the use of the smallest number that will allow valid information to be obtained from a study.

Refinement of animal sourcing, animal care practises and experimental procedures to minimise or remove physical and psychological distress, within the limitations imposed by the requirements of the research.

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

3.5 The ethical review process[8]

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 an Ethics Committee appointed by the Board of the MRC.

The duties of this Ethics Committee are to:

3.5.1 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;

3.5.2 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 ensure the availability of relevant sources of information which will facilitate these practises;

3.5.3 examine proposed experimental and teaching protocols submitted by institutional staff with reference to 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 weighted in relation to each other;

3.5.4 examine hypotheses to ensure they are well considered, plausible, and have a reasonable prospect of yielding good results;

3.5.5 approve applications that comply with the ethical principles for humane animal experimentation;

3.5.6 propose amendments and modifications, seek clarifications and request revised submissions in the case of the applications that are not approved;

3.5.7 reappraise applications that have not been completed within their proposed experimental period and reserve approvals for those in which there is no justification for time extensions;

3.5.8 consider the sourcing, care and accommodation standards applied to all animals within the institution, including breeding stocks, and monitor the humane killing of surplus animals;

3.5.9 regularly consult and engage with recognised authorities, concern groups and reputable sources of information to ensure that they are abreast of developments in the field of ethical review and analysis;

3.5.10 regularly review the establishment's managerial systems, procedures and protocols where these relate to the proper use of animals;

3.5.11 establish that both the 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; and

3.5.12 from time to time 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 among researchers and educators.

4. Ethical code of behaviour of researchers, educators and animal care staff

The following attitudes should apply to any programme in which laboratory animals are used.

4.1 The animal subjects

Sensitivity and respect for the sentience of non-human animals demands that they should be treated as organisms fully worthy of moral concern, under the stewardship of institutions and their staff.

4.2 Fairness and objectivity

Animal users should respect the interests of animals and not subject animals to intentions and motives which are not directly concerned with a research or teaching project, its objectives and its methodology.

4.3 Competence

Animal care staff, researchers and educators must be either professionally

and personally qualified and/or formally authorised by the South African Veterinary Council, if tasks deemed to be those pertaining to the Veterinary or Para-Veterinary Professions are to be performed. Professional standards shall be upheld in accordance with academic training and the requirements of the professional regulatory body which administers the Veterinary and Para-Veterinary Professions Act No. 19 of 1982.[9] The rules relating to the practising of the Para-Veterinary Profession of Laboratory Animal Technologist are appended to these guidelines as Annexure 1.

4.4 Responsibility

Researchers and educators who use laboratory animals and the staff who procure, breed and care for them are considered to be personally responsible for the proper care and use of these animals. They should uphold professional standards in accordance with their academic training and their professions.

4.5 Integrity

Integrity should be promoted by honesty and fairness. In particular, researchers, educators, animal care personnel and Ethics Committee for Research on Animals (ECRA) members should be honest about their own limitations, competence, belief systems, values and needs, and be prepared to respect views contrary to their own.

4.6 Sensitivity

Sensitivity in animal experimentation requires balancing scientific or teaching interests with general values and norms supporting the interests and welfare of the animal subjects. Special care should be taken not to treat animals as mere objects. Research objectives shall always be subordinate to the humane treatment of animals.

5. An ethical basis for using animals for research, teaching and education[10]

5.1 The moral issue of experimentation on humans and animals

Progress with medical and biological successes is based on research which ultimately must rest in part on experimentation involving human and animal subjects. The overriding ethical and legal constraints on invasive, potentially harmful and exploitative studies on humans regrettably necessitate a limited use of animal subjects, provided that this does not cause unnecessary suffering in the form of deprivation, fear, stress, distress and pain which may endure. Such conditions are addressed by refinement strategies to ameliorate them as far as it is possible to do so.

5.2 Present needs

Presently there is a continuing need for some animal experiments in both applied research and basic research aimed at extending human knowledge and heightening man's capacity to control his circumstances and protect human welfare. Some toxicological testing in animals is also still essential for medicine development and for the protection of consumers. This form of research often provides critical information that cannot be acquired from any other source or by any other means. However, likely adverse toxic or other effects on animals should be predicted. Where possible, they should be anticipated, and in the event of any observed adverse reaction, animal studies should be terminated at the earliest time so as to avoid unnecessary discomfort or suffering.

6. Human obligations and duties

6.1 Proper regulation of laboratory animal use

Animal users and institutional managements should strive for the best regulation of laboratory animal use at both an institutional and statutory level. They should see that animal welfare regulations and operational codes and practices are properly adhered to.

6.2 Public information

The availability to the public of regularly updated and good-quality information on what animal experiments are undertaken and why they are undertaken is vital to create circumstances in which the issue of animal experimentation can be productively discussed and debated.

6.3 Replacement of use of animals in research and education

With the rapid advances in science and technology there is increasing scope for the scientific community to contribute towards the development of non-animal methods of scientific investigation and teaching. It must be recognised that the ethical imperative of the 'replacement' component of the three Rs principles is a primary challenge in every animal use procedure, and forms a critical part of the analysis in the ethical review process.

7. A legal mandate for animal studies

7.1 The safety and efficacy testing of vaccines, medicines, medical appliances and materials, agricultural remedies, vaccines, nutritional supplements, pesticides and other consumer products is mandated by various Statutes in South African law. These laws are intended to promote the concept of preventative medicine which requires such substances to be

tested for safety and efficacy before they may be approved and registered for public use.

7.2 This mandate for animal studies is, however, not absolute, since progress is constantly being made in the development of methods for replacing animals in the safety testing of consumer products and medicines.

7.3 Any proposed use of animals for product safety testing must be preceded by a rigorous search for a validated animal replacement method. If such a method does not exist, then the proposal must be supported by a specific statement explaining why an animal experiment is necessary.

8. The ethical review process

8.1 Directive and policy

8.1.1 The Board of the MRC requires that an ethical review process be established and maintained both within the MRC and at every institution where MRC-supported animal studies are undertaken.

8.1.2 The performance of this institutional ethical review process is a precondition of MRC support, collaboration and co-operation.

8.2 Ethics Committee for Research on Animals (ECRA)

8.2.1 The ethical review process is to be performed by a designated ECRA.

8.2.2 The terms of reference of an ECRA are to:

i. monitor, inspect and assess the acquisition, transport, production, housing, care, use and disposal of animals;
ii. evaluate and approve, subject to possible modification, or reject written proposals for animal studies submitted for ethical review;
iii. regularly review operating standards and the ECRA's managerial systems, procedures, policies and protocols which relate to the proper care and treatment of research animals;
iv. report annually to the management of the institution;
v. advise how staff involved with animal production, care and teaching may be appropriately trained and how competence can be assured;
vi. withdraw approval for any approved project and/or authorise the humane killing formally of any animal which is being subjected to unnecessary deprivation, fear, distress and pain;
vii. maintain a register of approved projects and receive reports on their outcome; and
viii. recommend to the institution any measures needed to ensure that the standards of the National Code[11] are maintained.

8.3 Membership of an ECRA

8.3.1 An ECRA shall have a membership that will allow it to fulfil its terms of reference as defined in the SABS Code[11] and shall comprise at least six persons, including a separate person appointed to each of the categories which follow.

8.3.1.1 Category A

A person with qualifications in veterinary science, with experience relevant to the activities of the institution or, in special circumstances, a person with qualifications and experience to provide comparable expertise.

8.3.1.2 Category B

A person with substantial recent experience in the use of animals in scientific or teaching activities.

8.3.1.3 Category C

A person 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.

8.3.1.4 Category D

An independent person who does not currently and has not previously conducted scientific or teaching activities using animals, and who is not an employee of the institution.

8.3.1.5 Category E

A person responsible for the daily care of animals within the institution who should also be a member of the ECRA.

8.3.1.6 Category F

A person who has had formal training in biomedical ethics.

The committee may include additional co-opted members to ensure that it can function effectively.

8.3.1.7 The chairperson should hold a senior position in the institution.

8.3.1.8 If the committee has more than six members, Categories C plus D should represent no fewer than one-quarter of the members.

The composition of the ECRA must also comply with all relevant legislation.

8.3.2 Confidentiality

Before appointment, all members of the ECRA shall acknowledge in writing their acceptance of the terms of reference of the committee and any requirements for confidentiality required by the institution. The committee should reach agreement on how advice may be sought without breaching confidentiality.

8.3.3 Conflicts 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 either 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.

9. Form of application for ethical review

9.1 Written proposals

These should provide the ECRA with sufficient information to enable the committee to perform an ethical analysis and to conclude that the proposed use of animals is unavoidable, and that:

9.1.1 the use of animals is justified by a harm/benefit assessment;

9.1.2 the applicants are competent to perform the proposed studies;

9.1.3 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;

9.1.4 the project will be conducted in a responsible manner and at its conclusion will be formally reported on to the ECRA by the principal investigator; and

9.1.5 the application of the 'three R' principles of replacement, reduction and refinement will be evident in the proposed design and conduct of the study.

9.2 Form of proposal

Written proposals should be presented in a form that allows the ECRA easy access to information which is essential for ethical analysis, and written in such language and form that they can be comprehended by non-scientists who serve on an ECRA.

9.3 Checklist of information required for ethical analysis

Written proposals should contain the following information.

9.3.1 Project title

A short project title using keywords that best describe the study.

9.3.2 Applicants' profiles

The names, qualifications, institutional and departmental affiliations of persons applying for clearance to conduct the animal experiment together with background information on their past experience in animal experimentation should be given to provide some assurance of competence.

9.3.3 Co-workers

The names, qualifications and affiliations of all other co-workers involved with the proposed study are to be stated.

9.3.4 Declaration of principal investigator/educator

The signature of acceptance by the principal investigator of the *pro forma* MRC policy statement on:

i. the moral philosophy that supports animal experimentation;
ii. the recognition and acceptance of animal interests;
iii. the principles (the 'three Rs') of humane experimental technique;
iv. a requirement for relevance of the proposed research in the context of the MRC's objectives of advancing education, science, and human and animal welfare; and
v. 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
vi. a personal declaration of understanding and acceptance of the principles detailed above (i-v), an undertaking not to deviate from experimental protocol if and when it is approved by the ECRA, and an undertaking to report on the progress of the study at 6-month intervals once it has been started, as well as on its outcome when it has been completed.

9.3.5 Peer review statement

The application is to be supported by a peer review statement from either a Departmental, Faculty or Institutional Scientific Committee, 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.

9.3.6 Categorisation of the project

The proposed project is to be categorised in terms of its purpose, either to

educate or train students/staff or to do research. If animals are to be used for training purposes, the nature of the course and number of students to be trained is to be given. The proposed dates for starting and completing the study are to be given to indicate the required duration of the proposed study.

9.3.7 Background Information

A brief introductory statement (non-scientific summary) that explains what problems, questions, needs or new ideas have led to the planning of the experiment. A few key journal references may be included to substantiate viewpoints or premises.

9.3.8 Aims/objectives of the proposed study

The aim/s should be stated in brief sentences or as bullet points.

9.3.9 Potential benefits of the research findings or teaching exercise

Benefits arising from 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 man or animals or the environment. This enables the ECRA to weigh the 'harms' to the animals against the potential benefits which may arise from the results of the experiment. This procedure constitutes the formal 'cost (harm)/benefit analysis' which is central to the ethical review process. The term 'cost/benefit analysis' can be misleading if it is not understood in the context of ethical analysis. The 'cost' refers to the harm done to the animals and not to any financial cost. Parallels with cost/benefit analysis in a financial context may also suggest that the assessment is quantifiable, whereas in practice it is really a question of professional judgement. This assessment should rather be called a 'harm/benefit analysis' to promote a better understanding of what evaluation is being carried out.

9.3.10 Statement of hypothesis

If the proposed research project is of an explanatory nature rather than for gathering descriptive data, it is likely that an hypothesis is being tested. If this is so, the postulate should be simply and 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.

9.3.11 Animal requirements

The species, strain, gender, body mass, age and health (microbial) status of the proposed experimental animals and the total minimum number required for the experiment should be detailed. This information is important for defining the 'quality' of the proposed experimental system.

9.3.12 Justification of the need to use sentient animals and the 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 man 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.

9.3.13 Reduction of the number of animals to be used to a minimum

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

9.3.14 Animal caging and care

State 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.

9.3.15 Experimental design

Describe how the animals will be allocated by random selection to experimental and control groups, what experimental treatments will be assigned to each group, and at what frequencies these treatments will be applied.

9.3.16 Experimental procedure

Describe briefly in short numbered sentences all the steps to be performed in conducting the experiment, including operative procedures, collection of samples (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.

9.3.17 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.

9.3.18 Severity of the experimental procedures

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 in terms of frequency, severity and duration, e.g.

Procedure	***Outcome***
Mouse physically restrained	Transient fear
Mouse gavaged	Transient fear, discomfort, distress (5-8 seconds)
Mouse anaesthetised and laparotomy performed	Transient fear and minor pain of injection, transient distress on recovery from anaesthetic, mild postoperative discomfort for 1 day
Mouse inoculated with pathogen	Transient fear, mild pain on inoculation, followed by illness for 3 weeks with weight loss
Pig being anaesthetised to undergo arterial graft	Transient fear and distress until anaesthesia is attained, mild postoperative pain for 3-5 days: analgesia prescribed for 5 days. Mild transient fear and distress postoperatively with parenteral analgesia administration. Mild transient postoperative discomfort during wound healing for 7-10 days

The severity of the proposed procedure should be rated as minimal, intermediate or high on the basis of the criteria detailed below (adapted from the British Laboratory Animal Science Association's report on this aspect[13]).

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

Notes: Any procedures which are likely to cause severe deprivation, fear, illness, distress and pain that will endure or are likely to endure will ordinarily not be approved by the 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.

9.3.19 Fate of animals and their disposal at the end of the study

If this information has not been given earlier 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 is to be used, what humane rationale supports this choice, and how the animal carcasses are to be disposed of.

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

Detail of the route of substance administration and its dosage (mass or volume per body mass). The volumes of doses to be administered are also detailed for all medicinal and experimental substances.

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, and this responsibility be accepted by appending that person's signature to the application form.

9.3.21 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 (calculation of mean, standard deviation, standard error) and statistical evaluation (calculations of probabilities, tests of significance, determination of associations and correlations, etc.). If this analysis is to be done in collaboration with a statistician, state who that person is and what their institutional affiliations are.

9.3.22 Refinement of methodology to promote humaneness

Briefly and pertinently describe what steps have been taken to refine the experimental procedures 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, etc.).

9.3.23 Assurance of technical support and competence

Describe who will be responsible for the pre-, intra-, and postoperative/ experimental treatment care of the 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.

9.3.24 End-points for animal experiments that may cause illness and death of the animal

In studies in which illness or death of an animal may be an end-point (i.e. regulatory toxicology, diagnostic toxicology, acute toxicity studies in research, infections, disease studies, micro-organism virulence studies, vaccine efficiency trials, cancer research and cancer treatment, evaluation, etc.), discomfort should be alleviated by choosing the earliest end-point that is compatible with the scientific objectives of the research.[12]

If end-points are given, the applicant must submit a brief explanatory statement of why an end-point has been specified and what the humane basis for the selection of the end-point is.

The specification of end-points may have to be done in consultation with a laboratory animal veterinarian and the animal care committee.

The specification of end-points should also be supported by a statement of what detailed observations will be performed on the animals during the experimental period, together with a list of the most significant predicators of deterioration of the animal's condition and how these will be responded to by the investigators in deciding when to end observations and kill the animal.

It is expected that researchers will have reviewed the literature on this aspect in their field of study, and will be able to provide an observational protocol with a defined end-point which can be considered to be humane in terms of both the objective of the study and its potential benefit to humans, animals and the environment.

9.3.25 Biohazard statement

If the proposed study poses any hazards to either other laboratory animals or institutional staff arising from the handling and/or administration of infective agents, parasites, toxic or carcinogenic agents, or ionising radiation, a brief protocol for containing these hazards is to be provided. This should be supported by an approval statement from the Animal Unit Manager and Institutional Safety Officer, to provide assurance that the proposed project can be safely conducted. This statement should be signed by both of these officers.

9.3.26 Repetition

If the experiment or part of it is a repetition of previous work performed by the applicant or other persons, this is to be stated. If so, details are to be given and an explanation provided as to why the experiment or part of it that has previously been done is to be repeated to produce significant new knowledge.

10. Template of MRC's application form for ethical review by the ECRA (Annexure 2)

Application forms can be accessed from the MRC's website
http://www.sahealthinfo.org/ethics/index.htm

11. ECRA operating procedures

11.1 Appointment of Committee

After taking appropriate advice, the Board of the MRC shall formally appoint the ECRA.

11.2 Duration of membership

The period of membership of individuals may be prescribed, such as from 3 to 5 years, and may be renewed. It should be appreciated that members need time to absorb the ethos and develop the skills of ethical review.

11.3 Election of Chairperson and quorum

The Committee should elect its own Chairperson and Deputy Chairperson from among its members and should have a quorum of not less than five members.

11.4 Administrative support

The ECRA shall be supported by a Secretariat based within the MRC to perform its administrative duties, provide secretarial assistance, and maintain records of all ECRA documents and correspondence.

11.5 Meetings

The ECRA should meet four times a year at the MRC's Head Office at Medicina in Parowvallei, Cape Town, to review applications for ethical review and to conduct other business which falls within its terms of reference. The dates of meetings shall be set at the first ECRA meeting of each year. Notice of meetings and the agenda and working papers shall be sent to ECRA members to arrive at least 7 working days before the next meeting.

11.6 Chairperson's approval

The Chairperson may deal with minor matters with or without consulting the other members. Progress reports and the outcomes of all completed animal studies shall, however, be reported to all members at the next meeting of the Committee. Where possible, consensus should always be sought on urgent issues arising between meetings by electronic communication between the Chairman and ECRA members.

11.7 Co-options

The ECRA is empowered to co-opt additional non-scientist members and professional advisors onto the committee. Such co-options are to be approved by the Board of the MRC.

11.8 Recording of proceedings

Minutes shall be kept which record decisions and all other aspects of the ECRA's deliberations and business.

11.9 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 by 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. This documentation should be in the form of a checklist to assist in explicitly justifying the choices being made by the reviewing committee. The decisional system to be used is not prescribed. It may, however, be modelled on the decisional system proposed by Stafleu *et al.*[14] which is appended to these guidelines as Annexure 3.

11.10 Grant application approvals

Special consideration will be given to provisionally approving applications that are required to meet deadlines for grant applications. Such applications, which often propose a series of animal studies, may be provisionally approved subject to their having to undergo a further ECRA review after they have been successfully funded by granting agencies. These applications can be considered by e-mail consultation and communication between the Chairperson and Committee members in order to expedite their provisional approval. However, such provisional approval does not imply that after funding, permission has been granted by ECRA for the studies to proceed.

11.11 Communication with applicants

Researchers and teachers shall be informed of ECRA decisions in writing. No animal-based research, testing or teaching activities may commence before written ECRA approval has been received.

11.12 Adverse decisions and appeal

Although it is rare for a proposal to be judged to be totally unacceptable, it is common for projects to be modified on the advice of the ECRA. If an adverse decision is made, the reasons for this should be conveyed to applicants. They should also be made aware that they are entitled to have such a decision reviewed, and be invited to make written submissions and oral representations to the ECRA. If this is still not successful, the

applicants may request that the MRC either seeks external opinion or sets up an *ad hoc* committee to review the project and the decision.

11.13 ECRA register

A register of all approved projects, with their starting dates, 6-monthly reporting dates and end-of-project reporting dates shall be maintained.

11.14 Monitoring

It is not practical or even feasible for the ECRA to closely monitor the conduct of approved ongoing animal studies. This is a primary responsibility of the animal care staff and the Animal Unit Manager. However, the ECRA should not lose contact with applicants whose studies have been approved. Follow-up, in the form of monitoring replies to questionnaires sent to applicants, shall be done every six months. This will establish whether the project has been completed or abandoned (in which case a reason should be given), or is still in progress. In these questionnaires researchers and educators will be asked to certify that the animal studies are still being carried out according to the protocol. Any intended modification of the original protocol must be conveyed to the ECRA in writing, and approval thereof be obtained before it is implemented.

11.15 Reports

The ECRA shall report annually to the MRC Board on its membership and numbers of meetings held, and provide a list of titles of projects reviewed. The names of investigators will not be included in these reports. This report should be available for inspection by the public. The only exception to public inspection may be to protect commercial interests. A full record of such research and 6-monthly reporting on such projects must be kept by the ECRA secretariat.

12. Responsibility for the welfare of research workers, educators and technical support personnel

The ECRA stresses the importance of safeguarding the welfare of personnel participating in the research.

The principal investigator must apply safety rules and guidelines for the handling of hazardous materials, micro-organisms or parasites. In particular, the provisions of the Occupational Health and Safety Act No. 85 of 1993 regarding a safe working environment must be adhered to.

The ECRA stresses the importance of safeguarding the welfare of animals being held in laboratory animal facilities.

13. Responsibility for the welfare of laboratory animals confined within breeding and experimental holding facilities

Research Unit Directors/Managers must apply safety rules and guidelines for the preservation and protection of the health and welfare of laboratory animals when hazardous substances, micro-organisms or parasites are being worked with in experimental situations. In particular, the provisions of the Animals Protection Act No. 71 of 1962 must be observed.

14. Responsibility for compliance with statutes and provincial ordinances that specifically regulate some aspects of animal experimentation

The Director/Manager of animal research facilities shall have as a primary responsibility compliance with all laws and ordinances that regulate the acquisition, capture, importation, production, breeding, transportation, treatment, care and/or killing of laboratory animals and the acquisition, storage and use of hazardous substances, micro-organisms and parasites, including:

Animals Protection Act No. 71 of 1962
Animal Disease Act No. 35 of 1984
Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)
Medicines and Related Substances Control Act 101 of 1965
Veterinary and Para-Veterinary Professions Act No. 19 of 1982 (amended 1993)
The Provincial Nature Conservation Ordinances.

15. Responsibilities of researchers, educators and animal care personnel

15.1 The responsible researcher, educator and animal care staff are to be appropriately qualified and experienced and to have facilities to ensure that all procedures conducted on laboratory animals will be undertaken with due discretion and precautions to protect the welfare of the animals.

15.2 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.

15.3 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.

15.4 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.

15.5 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.

15.6 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.

16. Responsibilities of institutions whose staff receive MRC funding, collaboration and support for animal experimentation

16.1 It is required that all institutions receiving MRC support establish and maintain an ethical review process which conforms to these guidelines.

16.2 The exact nature of the process used will depend on the particular establishment and is not prescribed.

16.3 An appropriate structure of an ECRA is mandatory. A standard condition of MRC funding, collaboration and support is that a formal ethical review process has been performed in respect of all applications.

16.4 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, with non-sentient systems whenever possible, and to advise on the care and welfare of laboratory animals.

16.5 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 the conducting of 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. investigator responsibilities.

16.6 It is required that course participation and accreditation of all individuals who use animals in research, testing and teaching becomes mandatory, and that successful completion of institutional courses by individuals be recognised by the issuing of a certificate by the institution.

16.7 These courses will constitute research compliance training and may be a prerequisite for qualification for MRC funding for animal studies at both an institutional and personal level.

16.8 The exact nature of presentation of courses by an institution receiving MRC funding and requirements for examination and certification of persons who are to use animals for teaching, testing and education is not prescribed by the MRC.

17. References

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13. Working Party of the Laboratory Animal Science Association. The Assessment and Control of Severity of Scientific Procedures on Laboratory Animals. *Laboratory Animals* 1990; **24**: 97-130.
14. Stafleu FR, Tramper R, Vorstenbosch J, Joles JA. *A Decisional System for the Ethical Evaluation of Animal Experiments*. Utrecht University: Centre for Bioethics and Health Law, 1999.

18. Annexures

Annexure 1. Rules relating to the practising of the para-veterinary profession of Laboratory Animal Technologist (Notice 1445 of 1997 *Government Gazette*, 3 October 1997)

VETERINARY AND PARA-VETERINARY PROFESSIONS ACT, 1982 (ACT NO. 19 OF 1982)

It is hereby made known for general information that –

(a) the South African Veterinary Council has under section 30 (1) of the Veterinary and Para-Veterinary Professions Act, 1982 (Act No. 19 of 1982), made the rules relating to the practising of the para-veterinary profession of laboratory animal technologist as set out in the Schedule; and
(b) the Minister of Agriculture has under section 30(3) of the said Act approved the rules concerned.

H Kruger
Registrar: South African Veterinary Council

SCHEDULE

Definitions

1. Any word or expression in this Schedule to which a meaning has been assigned in the Act shall have that meaning, and –

"**animal experiment**" means any procedure whereby an animal is used in experiments for the purposes contemplated in rule 4.11;

"**experimental animal**" means non-human vertebrates and non-human vertebrate fetuses which are bred or acquired for the sole purpose of use as an animal experiment;

"**the Act**" means the Veterinary and Para-Veterinary Professions Act, 1982 (Act No. 19 of 1982); and

"**the profession**" means the para-veterinary profession of laboratory animal technologist.

SERVICES THAT PERTAIN TO THE PROFESSION OF LABORATORY ANIMAL TECHNOLOGIST

General services

2. For the purposes of the Act the following services shall be deemed to be general services which pertain to the para-veterinary profession of laboratory animal technologist:

2.1 care of experimental animals;
2.2 oral and parenteral administration and administration by inhalation of scheduled and experimental substances;
2.3 administration of scheduled substances for anaesthesia and euthanasia;
2.4 collection of body fluids including blood, urine by free flow and ascites, and the collection of tissues including smears, faeces, post mortal samples and bacterial swabs for diagnostic and experimental purposes;
2.5 clinical observation;
2.6 preparation of animals for surgery;
2.7 monitoring of animals before, during and after an operation;
2.8 performance of minor surgical procedures such as lancing of abscesses and suturing of superficial wounds;
2.9 assisting with experimental surgical procedures;
2.10 use of tranquilliser dart gun and blowpipe;
2.11 capture of wild animals for the purpose of research;
2.12 transportation of experimental animals;
2.13 training and examination of trainee laboratory animal technologists; and
2.14 teaching of students or researchers who require training in any specific aspect of laboratory animal technology.

Execution of general services

3.1 The services referred to in rule 2 shall –

(a) be carried out under the supervision of a veterinary or medical practitioner; and
(b) be performed on experimental animals only.

3.2 Rule 2 shall not be construed in a manner so as to prohibit –

(a) a veterinarian or a veterinary specialist from performing the services referred to in rule 2; and
(b) other para-veterinarians from performing procedures as set out for their profession.

Special services

4. For purposes of the Act the following services shall be deemed to be special services which pertain to the para-veterinary profession of laboratory animal technologist:

4.1 daily general care of laboratory animals;
4.2 management of various breeding programmes;
4.3 production of specified pathogen-free animals;
4.4 use and management of specialised animal house equipment;
4.5 maintaining and monitoring of animal house environment;
4.6 control of sanitation of hygiene in the animal house;
4.7 sterilisation and disinfection of the animal house and animal house equipment;
4.8 supervision over the feeding of experimental animals including the preparation of feed for special diets;
4.9 biohazard containment in the animal house including endogenous and exogenous containment;
4.10 general supervision, administration and use of laboratory animal facilities; and
4.11 conducting of experiments with experimental animals for any of the following purposes:

(a) the advancement of knowledge;
(b) to test a hypothesis;
(c) to supply a product;
(d) to provide organs, tissues or sera;
(e) to act as a host;
(f) to impart or demonstrate existing knowledge;
(g) to learn to teach surgical and other techniques;
(h) to comply with statutory requirements for testing or collecing data on any substance or product; and
(i) to make audiovisual recordings of any of the above.

Execution of special services

5.1 The services referred to in rule 4 shall be performed on experimental animals only.

5.2 Rule 4 shall not be construed in a manner so as to prohibit –

(a) a veterinarian or veterinarian specialist from performing the services referred to in rule 4; and
(b) other para-veterinarians from performing procedures as set out for their profession.

Code of conduct for persons practising the profession

6.1 A person who practises the para-veterinary profession of laboratory animal technologist shall base his or her personal and professional conduct thereon that –
(a) he or she is a member of a learned and honourable profession

who is required to act at all times in a manner that shall maintain and promote the prestige, honour, dignity and interests of the profession and of the persons by whom it is practised;

(b) he or she is morally obliged to serve the public to the best of his or her ability by maintaining at all times the highest standards of humane care of laboratory animals and professional conduct;

(c) he or she shall not seek any personal advantage at the expense of any colleague in the profession; and

(d) he or she shall not permit himself or herself to be exploited in a manner which may be detrimental to an animal, a researcher, the public or the profession.

6.2 A laboratory animal technologist shall –

(a) execute the instructions of a veterinarian discerningly and faithfully;

(b) refuse to take part in any unethical behaviour or procedure;

(c) keep himself or herself informed of all the statutes and statutory provisions which affect him or her in the practising of the profession;

(d) be familiar with the ethical rules pertaining to the profession of laboratory animal technology and shall promote these rules at all times;

(e) treat any information acquired during the course of his or her employment as strictly confidential and shall not divulge such information to any person except his or her employer;

(f) retrain from expressing any criticism in public through which the reputation, status or practice of a colleague in the profession is or could be undermined or injured, or through which a reflection is or could be cast on the probity, skill, methods or conduct of such a colleague; and

(g) at all times keep detailed and accurate records of all information and experiments and which shall be kept on file for at least five years.

6.3 All persons practising as laboratory animal technologists work for the same good cause and they shall therefore co-operate with each other and the authorities concerned to promote that cause.

6.4 The place at or from which a person practices as a laboratory animal technologist shall comply with the applicable minimum standards for experimental animals as determined by the Council from time to time.

6.5 When advertising of any nature is undertaken, a laboratory animal technologist must be aware of public opinion and of any possible implications which may prove detrimental to the profession of laboratory animal technology.

6.6 The fundamental responsibility of a laboratory animal technologist is to provide optimal and exemplary standards of humane animal care to experimental animals at all times.

Annexure 2. Application for ethical review of a proposal to use sentient animals (including their embryos and fetuses) for either research, teaching or testing (Application forms can be accessed from the MRC's website http://www.sahealthinfo.org/ethics/index.htm)

MEDICAL RESEARCH COUNCIL

ETHICS COMMITTEE FOR RESEARCH ON ANIMALS (ECRA)

APPLICATION FOR ETHICAL REVIEW OF A PROPOSAL TO USE SENTIENT ANIMALS (INCLUDING THEIR EMBRYOS AND FETUSES) FOR EITHER RESEARCH, TEACHING OR TESTING.

Application No.
To be allocated by ECRA

- This application must be typed.
- It must be signed by the Principal Investigator (the applicant) and other persons who are vouching for specialised aspects of the experimental design (i.e. statistician, safety officer, and persons responsible for supervising the use of scheduled medicinal substances.
- The application needs to be written simply, briefly and *is not to exceed* the framework of the spaces provided.
- The application should be mailed to the Secretary of ECRA, PO Box 19070, Tygerberg, 7505, or faxed to (021) 938-0200, to arrive before the MRC's quarterly deadline dates for submissions
- Telephone enquiries on any ECRA-related matters may be directed to either the Chairman or Secretary of the ECRA c/o MRC, at (021) 938-0911.

A. APPLICANT

Name:	Applicant's Title:	
Department:		
Tel. Nos: (w)	Fax:	Cell:
e-mail address:		
Qualifications	Appropriate Experience in Animal Research (Type of studies and years of experience)	

B. CO-WORKERS
(involved directly with procedures on animals)

Name:			
Department:			
Telephone Number:			
E-Mail address:			
Qualifications and/or SAVC Registration No.			
Appropriate experience in animal research			

C. OTHER CO-WORKERS
(Collaborators)

Name	Department/ Institution	Qualifications	Nature of involvement

D. ACCREDITATION COMPLIANCE

List the names (and accreditation numbers) of all the above persons who have successfully completed the institutional course of accreditation to use the institution's laboratory animal facilities and perform animal experiments.

	Name	Accreditation No.		Name	Accreditation No.
1.			5.		
2.			6.		
3.			7.		
4.			8.		

E. DECLARATION

1. Moral philosophy

The ethical review of proposed animal experiments is predicated upon the acceptance by the MRC that non-human animals are organisms fully worthy of moral concern, and as such their interests must be protected as far as possible in their use for advancement of biological knowledge and for the promotion of the health and welfare of animals and humans and the protection of the environment.

2. Animal interests

In the use of laboratory animals, animal interests obligate scientists and educators to:

- not allow animals to be used for research and/or to be killed for trivial, irrational, unjustified or inappropriate reasons;
- permit animals to live, reproduce and grow under conditions that are comfortable and reasonably natural to their species;
- keep animals free from disease, parasitism, injury and pain by prevention, rapid diagnosis and treatment;
- allow animals to be able express normal behaviour through providing as far as possible sufficient space, proper facilities in which to live and in the company of the animal's own kind, recognising their inherently social nature and hence the necessity of a social relationship for many species;
- protect animals from fear, deprivation, stress, distress and pain by ensuring that their living conditions, handling and treatment will be such that it will either minimise or eliminate the causation of these states upon those animals which are used for research, teaching and testing; and
- not unnecessarily repeat animal experiments the outcome of which are already known or are predictable.

3. Humaneness

The principles of humane experimental technique proposed by Russell & Burch must be followed in the planning and conduct of animal experiments.

These comprise:

– **Replacement** of animals with non-sentient research systems, i.e. researchers should strive to avoid using laboratory animals if alternative methods can yield the data they need.

– **Reduction** of the numbers of animals which are to be used to a minimum by design in order to achieve only sufficient statistical power to allow the objects of the experiment to be achieved.

– **Refinement** of the experimental methodology to be adopted by the implementation and if necessary the improvisation of procedures which will have the least distressing or harmful effect to the animals, and when this is not avoidable to counter those effects by the use of ataractics (tranquillisers), neuroleptics (dissociative agents), anaesthetics, analgesics and other effective strategies.

4. Animal protection

Animals should be protected from research designs which may cause pain, illness, isolation, mutilation (whether by surgery or otherwise) and/or premature death until such research can be demonstrated to be absolutely imperative and related to health, welfare and environmental problems which are potentially catastrophic in nature and for which alternative designs using non-sentient systems are not feasible.

5. Relevance

Animal-based teaching and research must address an important question relevant to the MRC's objectives in advancing knowledge, education, science and human and animal welfare through research, be based on a plausible hypothesis and have a reasonable prospect of yielding good results.

6. Responsibility

Everyone using animals, whether for experimentation, testing, diagnosis, teaching or sourcing of tissues or body fluids, is responsible in their personal capacity for assuring that the animals which they use are afforded the highest levels of welfare and protection from abuse, and violations of the interests accorded to them.

7. Personal declaration

7.1 I, (full name) ....., as Principal Investigator in this application, hereby declare that I am familiar with the precepts, policies and responsibilities outlined under Section E and will personally undertake to see that these are upheld in the conduct of this study, should it be approved.

7.2 I agree not to deviate from the approved protocol without obtaining ECRA clearance for any desirable or necessary changes that may need to be made in the methods used which may affect the welfare of the animal subjects.

7.3 In my opinion, all persons named and working under my supervision have the training and skills needed to carry out their responsibilities for experimental procedures, and the care and handling of the species being used.

7.4 I undertake to see that accurate and up-to-date clinical records are maintained on all experimental procedures performed on animals, and that daily records relating to their treatment, health and welfare are kept over the experimental period described in this study.

7.5 At the conclusion of the study I undertake to report on its outcome to the Animal Ethics Committee, and if it has not been completed within six months of it being cleared by the Committee, to submit progress reports at six-monthly intervals until the study has been completed.

....

Signature of Applicant **Date**

F. PEER REVIEW STATEMENT SUPPORTING THIS RESEARCH PROPOSAL

(Every application has to be supported by a declaration that it has undergone prior scientific review outside of the applicant's respective Unit or Group)

(tick answers [√])

I declare that this research protocol has been peer-reviewed by the

- ☐ Scientific Committee
- ☐ Faculty Committee
- ☐ External Review Committee
- ☐ Other ..... (specify which).....

of the (Institute/Unit) .....

on (date).....and has been judged to be relevant, designed in accordance with accepted scientific practices and norms, and is in the opinion of the reviewers likely to be successful in achieving its objective.

(Print name)

....

Signature, Chairman of reviewing body **Date**

G. PROTOCOL

1. Title of experiment or procedure:
(Use key words that specifically describe the animal experiment, and detail the animal species to be used)

2. NATURE OF PROJECT (tick applicable answers [√])

- ☐ New study
- ☐ Extension of approved project
- ☐ Amendment/s to approved project
- ☐ Research
- ☐ Training
- ☐ Production of biologicals for research/diagnosis/testing or other purposes (specify) .....

If training, for which course .....

No. of course participants .....

Source of funding for study .....

Expected starting date .....

Expected completion date .....

3. Background information

(Provide a brief introductory statement (a non-scientist's summary) that explains what problems, questions, needs or scientific or clinical observations or new ideas have led to the planning of the experiment. Include a few key journal references to substantiate viewpoints.)

4. Aim/s of the proposed study

(State these briefly and succinctly)

5. Potential benefits of the research findings

(These are required to aid the reviewing committee in performing a harm/benefit assessment)

6. Hypothesis

(If an hypothesis is being tested give the postulate/s (null hypothesis and alternates) to aid the reviewers in following the rationale of the proposed study)

7. Animal requirements

Animal species: .....

Strain: .....

Gender / Bodymass / Age: ..... // ...../// .....

Number required to achieve the purpose of this study: .....

Microbial status: .....

Source of animals: .....

8. Justification for the use of sentient animals

(Briefly justify the use of animals, the choice of species, the numbers to be used and, if there is limited availability or large numbers are to be used, provide additional rationale for their selection and numbers. State also what non-sentient model/s were considered and on what grounds they were rejected. Provide a brief narrative description of the methods and sources used to consider alternatives to the use of animals in this study.)

9. Reduction of number of animals to a minimum to achieve scientific objective

(Describe how this was determined, either by calculation (statistical design) or by specification (i.e. use of a validated testing protocol) or any other strategy)

10. Animal caging and care

(Briefly describe how the animals will be caged and what provisions have been made for their physical and psychological well-being, i.e. comfort, socialisation, behavioural needs and enrichment of their cage environment. Also state what provisions have been made to monitor the animals after they have been treated or undergone surgery, the frequency of observations, the behavioural and other signs being looked for which suggest illness, distress or pain, and state how they will be responded to.)

11. Statement of animal care competence, expertise and experience

(Provide a short statement of the scientific knowledge, competence and experience of the person appointed to ensure the comfort, health and humane treatment of the animal subjects in this study. If procedures specific to the practising of the Veterinary or Para-Veterinary Profession are to be performed in this study, authorisation by the South African Veterinary Council may need to be obtained as a prerequisite for this application. If this has already been done, name the authorised person and provide the authorisation number.)

12. Experimental design

(Describe how the animals will be allocated to experimental and control groups and, where applicable, how the experimental treatments will be assigned to each group)

13. Experimental procedure/s

(Describe briefly in short annotated sentences and in sequence all the steps that will to be performed in conducting the proposed experiment. These include: the arrangement of animals into groups, assignment of treatments to groups, selection of samples (if body fluids, give routes of collection and volumes), operative procedure, sampling procedure, parameters to be measured, data to be collected, outline of analysis to be performed, statistical tests, and probability level of confidence to be adopted (a non-scientist's summary is required).

14. Restraint of the animals

(Describe the methods of physical restraint (manual procedures and use of special restraint equipment) to be used on the animals and state who the animal handler/s will be)

15. Severity of effects of the experimental procedure on the animals

(List the procedures that may cause deprivation, fear, distress and pain and describe what sensations the animal may feel. Categorise these as minimal, intermediate or high (with reference to the abridged scale in the MRC's *Guidelines on Ethics for Medical Research* book 3: Use of Animals in Research and Training (point 9.3.18), for assessment of the severity of scientific procedures on animals derived from the report produced by the Working Party of the Laboratory Animal Science Association, *Laboratory Animals* 1990; **24**: 97-130). Give their likely duration in time. Describe what specific steps will be taken to alleviate these conditions through the use of ataractics, dissociative agents, analgesics, anaesthetics or other methods, and state how effective these are likely to be.)

16. Fate of animals and their disposal at the end of the study

(If this information has not been given earlier in this application, briefly state what the fate (rehabilitation and release, return to stock, euthanasia) of the group of experimental animals is to be at the end of the study, what method of euthanasia is to be used, what humane rationale supports this choice, and how the animals or animal carcasses are to be disposed of in a responsible and ecologically sound manner.)

17. Administration of scheduled medicinal substances (Medicines Control Act)

(List **all** substance administration to the animals and give routes of administration, dosages per body mass including anaesthetics, analgesics and euthanasing agents. State who is legally responsible for prescribing and directing the administration of the controlled Schedule 3 - 6 medicinal substances and other substances and provide their acceptance of this responsibility by signature.)

SUBSTANCE	ROUTE/SITE OF ADMINISTRATION	DOSE	FREQUENCY	TO BE ADMINISTERED BY

Responsible person (print name) .....

Qualification: .....

Acceptance signature: .....

Date: .....

18. Statistical analysis

(Describe briefly how the data obtained from the study will be analysed statistically and by whom the analyses will be performed)

19. Refinement

(Describe the specific steps that have been taken to refine the experimental procedures to make them as humane as possible, i.e. reducing numbers of animals and the severity of the experimental treatments on the animals)

20. Technical support and assurance of competence

(Describe who will be responsible for the pre, intra- and postoperative (or experimental period) care of the animals and give an indication of their experience and competence in monitoring clinical changes in the animals. Briefly state what clinical and behavioural criteria will be specifically monitored to assess the animals' well-being.)

21. End-points for experiments that induce illness in animals

(Give the end-points of data collection in experiments or procedures that may be expected to cause animals to become ill, lose weight, become distressed and experience pain. Justify these in terms of the needs of the experiment to attain its objectives.)

22. Identify the person/s who will be empowered to decide that a humane end-point has been reached in this study.

Name/s .....

Signature/s (denoting acceptance of this responsibility)

.....

23. Staff activities

(Describe (name and duties) the specific activity of each staff member who will be involved with the procedures)

24. Biohazard statement

(Does the project pose any hazards to other animals and staff from the use of either infective agents, toxic substances, carcinogenic agents or ionising radiation? If it does, state the specific safety procedures to be adopted to contain these hazards. Provide a brief approval statement below from the Institutional Safety Officer to provide assurance of safety for this project with this person's signature of ratification. If available, also append the laboratory's occupational safety protocol and/or standard operating procedures to promote safe practices and a safe working environment.)

Safety officer name (print): .....

Signature: .....

Date: .....

25. Repetition of experimental procedures

(Is this experiment a repetition of previous work performed by the applicant or others? If so, please give details and explain why the experiment is being repeated.)

Annexure 3. A decisional system for the ethical evaluation of animal experiments by Animal Research Ethics Committees (after Stafleu *et al.*[14])

FUNCTIONS OF THE SYSTEM

- **Checklist function:** The system provides a checklist of the normally relevant factors that should be considered and assessed.
- **A heuristic function (how to solve it):** The system focuses on the decision points. It demands an explicit justification of choices and shows the consequences of each choice.
- **A normative function (how to work it out):** The system enables a moral stance to be taken through assigning numerical weights to relevant issues as factors, and then using these values to compare the potential benefits to humans to the potential harm to animals in the proposed animal study.

THE PROCESS

The process comprises eight steps, as follows:

1. STATE THE GOAL AND POTENTIAL BENEFITS OF THE EXPERIMENT (ECRA Ref. No. .....).

Note: This is a statement of comprehension of the aims and rationale of the animal study by the ECRA. It is to be brief and succinct and made in non-scientific language, beginning with words: "This study or procedure is intended to .....". State what is being attempted, what outcome is being hoped for, and how this may impact scientifically in terms of either providing new information or information that may alleviate either human or animal suffering, mortality, or environmental harm, or how it may promote human or animal interests.

2. ASSESS AND SCORE HUMAN INTEREST INVOLVED IN THE ULTIMATE GOAL IN TERMS OF WELFARE, KNOWLEDGE AND ECONOMIC INTERESTS.

a) Score the human interest in terms of benefits to human and animal health and welfare and/or preservation and protection of the environment on a scale of 0 - 10.

(Can the findings of the study significantly contribute towards the prevention or alleviation of human or animal suffering, morbidity, or death, or halt or reverse ecological or environmental harm?)

HUMAN INTEREST (designated H) Score: H = _____ (0 - 10)

0 1 2 3 4 5 6 7 8 9 10 (possible scores)

Criteria for operationalising the above scale:

0 = no conceivable gains (e.g. Replication of existing research with no theoretical or methodological innovation. Minor educational value only)
5 = moderate gains likely (e.g. Some improvements in understanding, treatment, prevention of illness)
10 = highly important benefits likely (e.g. Prevention or treatment of a major health condition such as tuberculosis, diabetes, etc.)

b) Score the human interest in terms of potential gain of new scientific knowledge and its value to science on a scale of 0 - 5

(Can the findings of the study either lead to new hypotheses, or help to resolve or overcome problems worth solving?)

KNOWLEDGE INTEREST (designated K) Score: K = _____ (0 - 5)

0 1 2 3 4 5 (possible scores)

Criteria for operationalising the above scale:

0 = no scientific gains likely (e.g. Well researched and understood area of minor educational value only)
3 = moderate scientific gains (e.g. Refinement of existing knowledge or hypotheses)
5 = highly significant scientific gains (e.g. Potentially a major qualitative advance in theoretical sophistication)

c) Score the human interest in terms of the potential social and or economic benefits to humans and or animals on a scale of 0 - 5

(Can the findings of the study lead to benefits to either/or the national economy, industry, producers and consumers or impact positively on animal/environmental interests?)

ECONOMIC INTEREST (designated E) Score: E = _____ (0 - 5)

0 1 2 3 4 5

Criteria for operationalising the above scale:

0 = no conceivable benefits (e.g. Illustrative, academic or minor educational value only)

3 = some benefits likely (e.g. Some alleviation of economic hardship, especially for vulnerable or disadvantaged human populations. Economic improvement to non-human animals, such as especially vulnerable, exploited or endangered species may be evident as improvements in health, nutritional status, etc.)

5 = major benefits likely (e.g. Significant and sustained improvements to human and non-human populations with regard to the above considerations)

---

3. CALCULATE THE TOTAL INTEREST OF THE ULTIMATE GOAL (DESIGNATED IUG)

Use the formula that produces the **highest IUG score** (0 - 10) from one of the four following propositions:

(i) _____ (H) = _____ (IUG)

(ii) $\frac{\text{\_\_\_\_\_ (H) + (either \_\_\_\_\_(K) or \_\_\_\_\_ (E)) x 2}}{2}$ = _____ (IUG)

(iii) _____ (K) + _____ (E) = _____ (IUG)

(iv) $\frac{\text{\_\_\_\_\_ (H) + (\_\_\_\_\_ (K) + \_\_\_\_\_ (E))}}{2}$ = _____ (IUG)

4. ASSESS AND SCORE THE HUMANENESS AND RELEVANCE OF THE PROPOSED EXPERIMENT IN SIX STEPS (i - vi), AS FOLLOWS:

Score

(i) Is replacement with non-sentient animals possible? (0 or 10)	If Yes score **0** If No score **10 (i)** _____

(ii) Rate the general methodological soundness of the study (0 - 10)	If score **<7 score 0 (ii)** _____

0 1 2 3 4 5 6 7 8 9 10 (possible scores)

Criteria for operationalising the above scale:

0 = Unsound methodology (e.g. *Ad hoc* experimentation, casual clinical observations, poor or unreliable measures, etc.)

6 = Reasonable methodology, flaws apparent (e.g. lacking proper statistical controls, poor prospects for making inferences, inappropriate statistical model; *N* too low to achieve significance, etc.)

7 = Sound methodology, appropriate statistical model and controls, some improvements possible

10 = Rugged methodology, innovative design, well-considered statistical model (e.g. Original research design, likely to make a contribution to knowledge)

Note: Scores of 6 and 7 are effectively critical score thresholds.

(iii) Rate the application of humane experimental principles (application of the 3 Rs) (0 - 10)	If score **<7 score 0 (iii)** _____

0 1 2 3 4 5 6 7 8 9 10 (possible scores)

Criteria for operationalising the above scale:

0 = research subjects could be replaced by non-sentient systems, **OR** proposed study involves excessively large sample (when effect sizes are known, or may be estimated) **OR** procedures involve the infliction of physical and/or psychological

discomfort, restraints or loss of autonomy which is preventable

6 = some optimisation necessary for 3 R criteria to be met (e.g. It is clear that changes can be made in one or more areas to produce more satisfactory compliance)

7 = a reasonable balance is seen with regard to humaneness (3 Rs) and other considerations

10 = scrupulous attention has been given to the criteria and the proposed study is entirely convincing in terms of compliance with 3 R principles

(iv) Rate the necessity/relevance of the study to advance science and provide new knowledge (0 - 10) If score **<5 score 0 (iv)** _____

0 1 2 3 4 5 6 7 8 9 10 (possible scores)

Criteria for operationalising the above scale.

0 = study is redundant, or irrelevant and no advances are likely to be realised

4 = research replicates previous studies without refinement, or the research rationale is unconvincing in terms of the potential for producing new knowledge

5 = research has a reasonable prospect of generating scientific advances

10 = research has clear potential to generate valuable scientific advances

(v) Rate the probability of a successful outcome (0 - 10) Score **0 to 10 (v)** _____

0 1 2 3 4 5 6 7 8 9 10 (possible scores)

Criteria for operationalising the above scale:

0 = no likely prospect of research succeeding

4 = prospects are somewhat doubtful

5 = reasonable prospect of success

10 = virtual certainty of success

(vi) Rate the quality of the research group proposing the study (0 - 10) If score **<5 score 0 (vi)** _____

0 1 2 3 4 5 6 7 8 9 10 (possible scores)

Criteria for operationalising the above scale:

0 = unqualified, non-accredited or unsuitable personnel

4 = problems are known to exist with group: e.g. known problems with track record, reputation, capacity, objectivity, or ability to conduct acceptable research

5 = no reservations about group's capacity to conduct scientific research

10 = experienced, highly rated group with excellent scientific and moral credibility

Then calculate the relevance and humaneness score (designated R)

Total score sum of $\frac{\text{(i) to (vi)}}{60}$ = _____ (R)

Note: If R is less than 0.65 the proposal will be deemed to be inadmissible.

---

5. CALCULATE THE HUMAN INTEREST (DESIGNATED HI) COMPONENT INVOLVED IN THE EXPERIMENTS

Interest of ultimate goal (IUG) value x relevance (R) value = HI

_____ (IUG) x _____ (R) = _____ HI

(Possible score 0 - 10)

---

6. ASSESS AND SCORE THE HARM TO ANIMALS' INTERESTS IN THE PROPOSED STUDY

(i) **Actual discomfort to single animal subjects (designated A, range 0 - 4)**

None	=	0
Slight	=	1
Moderate	=	2
Severe	=	3
Very severe	=	4

A = _____

(ii) **Duration of discomfort to single animal subjects (designated D, range 0 - 2)**

Short or none	=	0
Medium and/or frequently	=	1
Long-lasting and/or Very frequently	=	2

D = _____

(iii) **Number of animals to be killed in study (designated N, range 0-2)**

<10 animals	=	0
10 - 100 animals	=	1
>100 animals	=	2

N = _____

(iv) **Calculate total discomfort (designated T, range 0 - 6) using the following formula:**

$$A + \frac{D + N}{2} = T \text{ (possible score 0 - 6)}$$

$$\_\_\_\_\_ + \frac{\_\_\_\_\_}{2} = \_\_\_\_\_ \text{ (T)}$$

(v) **An intrinsic value of 2 (designated IV) is accorded as an additional weighting value for the animal interest.**

(vi) **Psychological complexity of the animals (designated P).**

P = Species Considerations (SC) + Sociability of Species (SS)

Species Considerations Scores		**Sociability Scores**	
Non-human primates	= 1	Highly gregarious	= 1
Other vertebrates	= 0.5	Moderately gregarious	= 0.5
Cold-blooded animals	= -2	Solitary species	= 0

(SC) ____ + (SS) _____ = _____ (P) (possible scores = -2 to +2)

---

7. CALCULATE THE HARMED EXPERIMENTAL ANIMAL'S INTERESTS, DESIGNATED AI, USING THE FORMULA:

Total discomfort (T) + (IV = 2) + Psychological complexity (P) = Animal Interest (AI)

(T) _____ + 2 + (P) _____ = _____ AI
(Possible score = 0 - 10)

---

8. ASSESS THE ETHICAL ACCEPTABILITY OF THE EXPERIMENT BY COMPARING HUMAN INTEREST (HI) (BENEFIT) VERSUS THE ANIMAL INTEREST (AI).

If the Human Interest (HI) _____ ≥ _____ the Animal Interest (AI) the experiment **is admissible**.

If the Human Interest (HI) _____ < _____ the Animal Interest (AI) the experiment **is inadmissible**.

Signed: ..... Chairperson of Animal Ethics Committee

Print name: .....

Date: .....

Note: The Decisional system can be abbreviated and be scored and assessed on a single A4 page. In this booklet we have condensed it into 2 pages, overleaf. A single-page template can be obtained on the MRC's website, http://www.sahealthinfo.org/ethics/index.htm

ETHICAL ANALYSIS OF A PROPOSAL FOR USE OF ANIMALS FOR RESEARCH, TESTING AND TEACHING

APPLICATION NO: **PRINCIPAL INVESTIGATOR:**

TITLE:

1. Goal and potential benefits of the experiment or procedure.

2. Human, Knowledge and Economic Interests.

H = ☐ (0 - 10) K = ☐ (0 - 5) E = ☐ (0 - 5)

3. Total Interest of Ultimate Goal (IUG)

(i) H = ☐ IUG

(ii) $\frac{H + (\text{either } K \text{ or } E) \times 2}{2}$ = ☐ IUG

(iii) K + E = ☐ IUG

(iv) $\frac{H + K + E}{2}$ = ☐ IUG

Highest IUG Score ☐ (0 - 10)

4. Humaneness and Relevance (R)

(i) Non-sentient replacement	(0 or 10)	_____
(ii) Methodological soundness	(0 - 10)	_____
(iii) Application of 3 Rs	(0 - 10)	_____
(iv) Necessity/Relevance of study	(0 - 10)	_____
(v) Probability of successful outcome	(0 - 10)	_____
(vi) Quality of research group	(0 - 10)	
TOTAL:		_____

Calculate $\frac{\sum \text{ i to vi}}{60}$ = ☐ (R)

Is R > 0,65? If not, the study is inadmissible, if > 0,65 continue with the analysis.

5. Calculate Human Interest.

IUG ____ x ____ R = [ ] HI

---

6. Assess and score the Harm to Animal Interest.

Deprivation, discomfort, fear, distress, pain to a single animal (A)		**Duration of discomfort (D)**		**No. of animals in study to be killed (N)**	
None	0	Short or None	0	< 10	0
Slight	1	Medium & frequently	1	10 - 100	1
Moderate	2	Long lasting & Very frequently	2	> 100	2
Severe	3				
Very severe	4				
A = _____		D = _____		N = _____	

Calculate total discomfort (T) $\frac{A}{} + \frac{D + N}{2}$ = [ ] T (0 - 6)

Psychological complexity (P)		**Sociability Scores (SS)**	
Species (SP): Non-human primates	1	Highly gregarious	1
Other vertebrates	0.5	Moderately gregarious	0.5
Cold-blooded animals	-2	Solitary species	0
SP = [ ]		SS = [ ]	

SP_____ + SS _____ = [ ] P

---

7. Calculate the Harmed Animal Interest (AI).

T_____ + 2 (IV) + _____ P = [ ] AI (0 - 10)

---

8. Ethical Judgement.

HI [ ] ≥ [ ] AI = [ ] Admissible (tick)

HI [ ] < [ ] AI = [ ] Inadmissible (tick)

Signature ..... Chairperson of ECRA

Date: .....

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