ANNEXURE 1

**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 FOETUSES) 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 emailed to ECRA’s Scientific Review Committee (zandisiwe.magwebu@mrc.ac.za), to arrive before the SAMRC’s quarterly deadline dates for submissions – for deadline dates, please see <http://www.mrc.ac.za/research/ethics/ethics-committee-for-research-on-animals>.
* Enquiries on any ECRA related matters may be directed to the Secretariat, c/o Adri Labuschagne on 021-938 0687 or [Adri.Labuschagne@mrc.ac.za](mailto:Adri.Labuschagne@mrc.ac.za)

**DATE OF SUBMISSION:**

FOR OFFICE USE ONLY.

# A. APPLICANT

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Name** |  | | | | | | | | **Title** |  |
| **Institution** | |  | | | | | | | | |
| **Department/Division** | | | | |  | | | | | |
| **Tel. No.** | | | **Work:** | | | | **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** |  |  |  |
| **Institution** |  |  |  |
| **Department/**  **Division** |  |  |  |
| Telephone **number** |  |  |  |
| **E-mail address** |  |  |  |
| **Qualifications**  **and/or SAVC**  **Registration No.** |  |  |  |
| Appropriate **experience in**  **animal research** |  |  |  |

**C. OTHER CO-WORKERS. (Collaborators)**

|  |  |  |  |
| --- | --- | --- | --- |
| **NAME** | **INSTITUTION/**  **DEPARTMENT** | **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 institutional laboratory animal facilities and perform animal experiments.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | NAME | ACCREDI- **TATION NO.** |  | NAME | ACCREDI- **TATION 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 protection of the environment.

1. **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 the 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.
* not unnecessarily repeat animal experiments the outcome of which is already known or is predictable.

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

1. **Animal Protection**

Animals should be protected from research designs which involve 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.

1. **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 plausible hypothesis and have a reasonable prospect of yielding good results.

1. **Responsibility**

Everyone using animals, whether for experiments, 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.

1. **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.

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.

In case any unexpected adverse effects of the approved methods used, or drugs administered to the animals are detected, it will immediately be reported to the laboratory animal technologist and communicated to the ECRA secretariat.

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.

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, care and handling of the species being used.

…………………………………… ………………………

**Signature of Applicant Date**

**F. PEER REVIEW STATEMENT.** (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).

I declare that this research protocol has been peer reviewed by the (tick answers √ )

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. **Project Title:**
2. **Nature of Project (tick applicable answer √ )**

New Study

Extension of approved project

Amendment/s to approved project

Research

Training

If training, for which course : …………………………………………………………….

No of course participants : …………………………………………………………….

Source of funding for Study : …………………………………………………………….

Expected Starting Date : …………………………………………………………….

Expected Completion Date : …………………………………………………………….

1. **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.)

1. **Aim/s of the Proposed Study**

(State these briefly and succinctly.)

1. **Potential Benefits of the Research Findings**

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

1. **Hypothesis**

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

1. **Animal Requirements**

Animal Species: …………………………………………………………………….

Strain: …………………………………………………………………….

Gender / Body mass / Age: ………………….// ………………………// ………………

Number Required to achieve the purpose of this study: …………………..

Microbial Status: …………………………………………………………………………

Source of Animals: ………………………………………………………………………

1. **Justification for the use of sentient animals.**

(Briefly justify the use of animals, the choice of species, the numbers to be used and if these 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.)

1. **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.)

1. **Animal Caging and Care**

(Briefly describe how the animals will be caged and what provisions have been made for the physical and psychological wellbeing i.e. comfort, socialisation, behavioural needs and enrichment of their cage environment.)

1. **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 a 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 pre-requisite for this application. If this has already been done, name the authorised person and provide the authorisation number.)

1. **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.)

1. **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, the 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, probability level of confidence to be adopted (a non-scientist’s summary is required.)

1. **Restraint of the Animals**

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

1. **Severity of Effects of the Experimental Procedure on the Animals and Category of Invasiveness**

(List the procedures that may cause deprivation, fear, distress and pain and describe what sensations the animal may feel. Rate the anticipated sensation as a severity score (see Severity Scale in *Annexure A* or see ECRA SOP on SAMRC website). Give their frequency and 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 estimate how effective these are likely to be as minimal, moderate or high. Select the appropriate category of invasiveness (A-E) (from ECRA Invasiveness Categories in *Annexure B*) which is deeming to fit the entire study.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Procedure** | **Anticipated sensation** | **Severity score** | **Frequency & Duration** | **Steps to alleviate** | **Anticipated effectiveness** |
|  |  |  |  |  |  |
| **Category of invasiveness for entire study** | |  | | | |

1. **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 animals carcases are to be disposed of in a responsible and ecologically sound manner.)

1. **Administration of Schedules 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 euthanazing agents. State who is legally responsible for prescribing and administration of the controlled Scheduled 3 – 6 medicinal substances and other substances and provide their acceptance of this responsibility by signature.)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **SUBSTANCE** | **ROUTE/SITE OF ADMINISTRATION** | **DOSE** | **VOLUME** | **FREQUENCY** |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

Person *prescribing* substance(s): …………………………………………………………………

Qualification: …………………………….

Acceptance signature: ………………………………………… Date: …………………………………………

Person *taking responsibility for administration of* substance(s): ……………………………………

Qualification: …………………………….

Acceptance signature: ………………………………………… Date: …………………………………………

1. **Statistical Analysis**

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

1. **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.)

1. **Technical Support and Assurance of Competence**

(Describe who will be responsible for the pre, intra- and post-operative (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 animal’s wellbeing.)

1. **Endpoints and Interventions for Experiments that Induce Illness in Animals**

(Give the endpoints of data collection in experiments or procedures that may cause animals to become ill, lose weight, become distressed and experience pain. In addition, provide interventions that may need to be performed to maintain animal welfare before such endpoints are reached, as well as when they will be instituted. Justify these in terms of the needs of the experiment to attain its objectives. Provide *both* a daily monitoring sheet and a description of humane end points. )

1. **Staff Activities**

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

1. **Biohazard Statement**

The PI 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. 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 MRC/institutional accredited waste disposal companies, and (b) guarantees an appropriate waste disposal budget for the project.

The signature below testifies that the PI takes fully responsibility for all above and that every reasonable measure has been taken to contain hazards.

Name of Principle Investigator (Print): ………………………………………………..

Signature: ………………………………………………..

Date: ………………………………………………..

Signature (where applicable) of Radiation Protection Officer or Acting Radiation Protection Officer with authority for the appropriate isotope:

Radiation authority number : ………………………

1. **Repetition of Experimental Procedures**

(Is this experiment a repetition of previous work performed by the applicant or others.

If yes, please give details and explain why the experiment is being repeated.)

**ANNEXURE A**

**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***  Mucous membranes 4  Skin 3 Eye 6  Scarifying skin 11 | ***Blood***  Venepuncture 5  Venesection 8  Orbital sinus 11  Tail prick 9 | Skin incision 3  Skin graft 10  Skin biopsy 3  Laparotomy 9  Thoracotomy 11  Adrenalectomy 9 | ***Whole body***  Continuous 18  Discontinuous 12  Crush cage 9 |
| ***Injection***  Intradermal 7  Subcutaneous 3  Intramuscular 4  Intravenous 4  Orbital sinus 11  Intra-lymphatic 7  Intra-peritoneal 5 | ***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 | Lymphadenectomy  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 superficial 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  Venesection 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 |  |  |
|  | ***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.

**ANNEXURE B**

**Categories of invasiveness in SAMRC animal experiments**

The five categories of invasiveness are defined as follows:

1. Most invertebrates or live tissue
2. Little or no discomfort or stress
3. Minor stress or pain of short duration
4. Moderate to severe distress or discomfort
5. Severe pain near, at, or above the pain tolerance threshold of unanaesthetized, conscious animals

In the tables below are examples of experimental procedures which are to be considered representative of the five categories of invasiveness.

**Category A: Most invertebrates or live tissues**

|  |  |
| --- | --- |
| **Description** | **Possible examples** |
| Studies or experiments on most invertebrates, or on non-entire living tissues.   * Cephalopods and other higher invertebrates have nervous systems as well-developed as some vertebrates and in such cases Categories B**-**E should apply | * Use of tissues obtained at autopsy, necropsy or from the slaughterhouse * Use of vertebrate eggs (<50% development), protozoa and related single-celled organisms * Studies or experiments involving containment or other non-invasive action on metazoa |

**Category B: Little or no discomfort or stress**

|  |  |
| --- | --- |
| **Description** | **Possible examples** |
| Procedures with no significant impairment of the wellbeing or general condition of the animals. | * Domestic flocks or herds being maintained in simulated or actual commercial production management systems * Short periods of food and/or water-deprivation equivalent to periods of abstinence in nature * Injection of materials, not more than 3 times per week in amounts that will not cause adverse reactions by the following routes: intravenous, subcutaneous, intramuscular, intraperitoneal, or oral, but NOT intrathoracic or intracardiac (these fall under Category D) * Acute non-survival studies in which the animals are completely anesthetized and do not regain consciousness * Approved methods of euthanasia following rapid unconsciousness such as anesthetic overdose or decapitation |

**Category C: Minor stress or pain of short duration**

|  |  |
| --- | --- |
| **Description** | **Possible examples** |
| Procedures on animals as a result of which the animals are likely to experience short term mild pain, suffering or distress.   * During or after Category C studies, animals must not show self-mutilation, anorexia, dehydration, hyperactivity, increased dormancy, increased vocalization, aggressive defensive behaviour or demonstrate social withdrawal and self-isolation. | * Studies involving short-term (< month) deprivation of social partners or solitary caging of adult rats or mice of sociable strains * Withdrawal of food for 8-12 hours in adult mice, 12 hours in adult rats and 12-16 hours for adult primates * Feeding of modified diets, that do not meet all of the animals' nutritional needs and are expected to cause mild clinical abnormality within the timescale of the study * Short term (<24h) restraint in metabolic cages * Evoking escape and avoidance reactions where the animal is unable to escape or avoid the stimulus and are expected to result in minor distress (depend on stimulus and species) * Non-invasive imaging of animals (e.g. MRI) with appropriate sedation or anesthesia * Application of external telemetry devices that cause only minor impairment to the animals or minor interference with normal activity and behaviour * Models which expose animals to noxious stimuli which are briefly associated with mild pain, suffering or distress, and which the animals can successfully avoid * Administration of substances 4-14 times per week and not more than 3 times per day (for one day) depending on the route of administration (e.g. subcutaneous: 2x per day; intramuscular: 1x per day; intraperitoneal: 1x per day; gavage: 1x per day and intravenously via superficial blood vessels: 1x per day), where the substance has no more than mild impact on the animal, and the volumes are within appropriate limits for the size and species of the animal * Pharmacokinetic study where a single dose is administered, and a limited number of blood samples are taken (totaling <7.5% and < 10% of circulating volume over a period of 1 and 4 weeks respectively) and the substance is not expected to cause any detectable adverse effect * Superficial procedures, e.g. ear and tail snips in rats (acceptable size will depend on size of animal), non-surgical subcutaneous implantation of mini-pumps and transponders * Cannulation or catherization of blood vessels or body cavities under anesthesia, such as biopsies and laparoscopy * Induction of tumors, or spontaneous tumors, that cause no detectable clinical adverse effects (e.g. small, subcutaneous, non-invasive nodules) * Breeding of genetically altered animals which is expected to result in a phenotype with mild effects, e.g. db/db mice |

**Category D: Moderate to severe distress or discomfort**

|  |  |
| --- | --- |
| **Description** | **Possible examples** |
| Procedures on animals as a result of which the animals are likely to experience short term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress.  Procedures that is likely to cause moderate impairment of the wellbeing or general condition of the animals.   * Procedures used in Category D studies should not cause prolonged or severe clinical distress as may be exhibited by several clinical signs, such as marked abnormalities in behavioral patterns or attitudes, the absence of grooming, prolonged anorexia, dehydration, abnormal vocalization, circulatory collapse, extreme lethargy or reluctance to move, and clinical signs of severe or advanced local or systemic infection. | * Isolation for prolonged periods of social species e.g. dogs and non-human primates, but including some contact with conspecifics * Withdrawal of food for 16 hours in adult mice and 24hours in adult rats and small primates, and 48hr in medium sized primates * Studies with modified diets that do not meet all of the animals’ nutritional needs and are expected to cause moderate clinical abnormality within the timescale of the study * Use of metabolic cages involving moderate restriction of movement over a prolonged period (up to 5 days) * Frequent application of test substances which produce moderate clinical effects, and withdrawal of blood samples (>10% of circulating volume) in a conscious animal within a few days without volume replacement. Maximum blood collection allowed: 15% once off of circulating volume, or 20% if removed in multiple samples over 24 hours, after which a 4 week recovery period is needed * Administration of substances under anesthesia via intrathoracic or intracardiac routes * Acute dose-range finding studies, chronic toxicity / carcinogenicity tests, with non-lethal endpoints * Surgery under general anaesthesia and appropriate analgesia, associated with postsurgical pain, postoperative analgesia, suffering or impairment of general condition. Examples include thoracotomy, craniotomy, laparotomy, orchidectomy, lymphadenectomy, thyroidectomy, orthopaedic surgery with effective stabilization and wound management, organ transplantation with effective management of rejection, surgical implantation of catheters, or biomedical devices (e.g. telemetry transmitters, minipumps, etc.) * Models of induction of diseases (e.g. SHIV, SIV) and tumors, including spontaneous tumors, that are expected to cause moderate pain or distress or moderate interference with normal behaviour * Irradiation or chemotherapy with a sublethal dose, or with an otherwise lethal dose but with reconstitution of the immune system. Adverse effects would be expected to be mild or moderate and would be short-lived (<5 days) * Breeding of genetically altered animals which are expected to result in a phenotype with moderate effects * Creation of genetically altered animals through surgical procedures | |

**Category E\*: Severe pain near, at, or above the pain tolerance threshold of unanesthetized conscious animals**

|  |  |  |
| --- | --- | --- |
| **Description** | **Possible examples** | |
| Procedures on animals as a result of which the animals are likely to experience severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress.  Procedures which are likely to cause severe impairment of the wellbeing or general condition of the animals. | | * Complete isolation for prolonged periods of social species e.g. dogs and non-human primates * Use of metabolic cages involving severe restriction of movement over a prolonged period * Inescapable electric shock (e.g. to produce learned helplessness) * Forced swim or exercise tests with exhaustion as the end point * Testing of a device where failure may cause severe pain, distress or death of the animal (e.g. cardiac assist devices) * Toxicity testing where death is the endpoint, or fatalities are to be expected and severe pathophysiological states are induced. For example, single dose acute toxicity testing (see OECD testing guidelines) * Vaccine potency testing characterized by persistent impairment of the animal’s condition, progressive disease leading to death, associated with long-lasting moderate pain, distress or suffering * Surgical and other interventions in animals under general anaesthesia which are expected to result in severe or persistent moderate postoperative pain, suffering or distress or severe and persistent impairment of the general condition of the animals. * Organ transplantation where organ rejection is likely to lead to severe distress or impairment of the general condition of the animals (e.g. xenotransplantation) * Production of unstable fractures, thoracotomy without adequate analgesia, or trauma to produce multiple organ failure * Models with induction of tumors, or with spontaneous tumors, that are expected to cause progressive lethal disease associated with long-lasting moderate pain, distress or suffering. For example, tumors causing cachexia, invasive bone tumors, tumors resulting in metastatic spread, and tumors that are allowed to ulcerate * Immobilization stress to induce gastric ulcers or cardiac failure in rats Irradiation or chemotherapy with a lethal dose without reconstitution of the immune system, or reconstitution with production of graft versus host disease * Breeding animals with genetic disorders that are expected to experience severe and persistent impairment of general condition, for example Huntington’s disease, muscular dystrophy, chronic relapsing neuritis models | |

\* ECRA will require a strong and acceptable justification for Category E studies to be performed at the SAMRC or collaborative institutions