Applying for the use of experimental animals in FOTS, guidance document.

This document represents the experience of KPM on good and below standard ethical applications, and guidance about what the Norwegian Food Safety Authority (Mattilsynet or MT) will expect from an ethical application. This document follows the heading titles (A-I) and subtitles (1-x) found in the electronic version of FOTS.

The named animal care and welfare officer (Person med særskilt kontrollansvar, PMSK) performs the local evaluation. The form used by PMSK for local evaluation and feed-back to the applicant is enclosed at the end of this document. Mattilsynet will authorize the use of research animals based on the ethical applications submitted in FOTS. When initiated, each ethical application obtains a unique number code, also known as the FOTS-id. The relevant heading title and subtitle is referred to in comments when deficiencies are indicated by local evaluation. After evaluation applications with deficiencies is put to draft and the applicant is informed that the application will not be sendt to MT until all defiencies are corrected. If the deficiencies after resubmission are not adequately addressed when, the application is put back in draft so that the applicant can make the necessary corrections.

An English version of FOTS can be chosen during log-in by clicking on the English flag.

Applying for ethical approval in FOTS, new experiments

A General information

1 Working title:
2 Application summary: *The application summary will be published by MT and must not include sensitive information related to IP, or scientific interests or information that is otherwise intended to be exempt from public access. Use lay terms for a general description of the project/experiment. Maximum 500 words. The summary must describe the following:* *1. Project objective* *2. Harm* *3. Predicted benefit* *4. Numbers and types of animals to be used* *5. How to comply with the 3Rs*
3. Establishment where the experiment/project will be conducted: *The link between the applicant and the institution will be decided by the FOTS user name and password that was used for FOTS access.*
4 Application category: Pilot experiment / New experiment / Extension/Change
5 Field experiment, including localization and scientific justification: *Experiments outside approved facilities. Not relevant at OUS.*
6 Multiple generic projects: *Only relevant when the project is necessary to satisfy regulatory requirements, or us animals for production or diagnostic purposes with established methods (§ 6. 5. paragraph). Not relevant for research purposes.*
7 Severity category and reasons for the chosen category: *Non-recovery / mild / moderate / severe experiments. The applicant must prospectively evaluate and classify the experiment(s) according the degree and duration of pain, fear, lasting harm or other adverse effects. Individual <u>cumulative</u> severity for the most affected animals during the procedure, the type of handling and/or lack of ability to*

express natural behavior (including restricted standards of housing and care), and the possibility of recovery between procedures must be incorporated in the evaluation. The maximum cumulative severity for individual animals is to be stated. Note that evaluation of severity classification includes more parameters than just pain. Please note that experiments that will result in long lasting severe pain, fear or other adverse effects, that cannot be ameliorated, is not allowed (§ 13).
Experiments are characterized into the following 4 severity categories: Non-recovery, Mild, Moderate and Severe. See Forsøksdyrforskriftens Vedlegg B, where examples on experiments in the different categories are listed. The severity categories are defined as follows:

I. *Non-recovery: Procedures which are performed entirely under general anesthesia from which the animal shall not recover consciousness.*
II. *Mild: Procedures on animals as a result of which the animals are likely to experience short-term mild pain, suffering or distress, as well as procedures with no significant impairment of the well-being or general condition of the animals.*
III. *Moderate: 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 as well as procedures that are likely to cause moderate impairment of the well-being or general condition of the animals.*
IV. *Severe: 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 as well as procedures, that are likely to cause severe impairment of the wellbeing or general condition of the animals*

It is noted that many FOTS-applications indicate unrealistic assessments of the severity and longevity of pain and adverse effects, notably by not considering the cumulative effects of multiple procedures. The applicant is advised to assess the severity classification realistically and seek advice from PMSK if needed.

8 Previous experience with comparable procedures: *No/Yes. It is relevant and recommended that the applicant includes the experience of the applicant and all participants when answering this question*

9 Experiments/procedures funded by: Den *Norske Kreftforening/ EU/EØS-midler/ Forskningsrådet/På oppdrag fra offentlig etat/På oppdrag fra privat bedrift/ Annen finansieringskilde. All applications are expected to hold the same quality, irrespective of funding source. Applications supported by large and important funding institutions are sometimes seen to have very brief, sometimes even incomplete, applications. While funding by EU and/or Forskningsrådet obviously is an indicator of relevance, it is important to realize that funding from these sources does neither constitute an approval nor an evaluation of specific experimental animal projects.*

10 Planned start and end dates: *The applicant is advised to apply for sufficient project time. Projects tend to take more time than planned, the approved project time is without any ethical consequence and all applications (including applying for extension) will be invoiced by MT. Applications can be approved for up to 4 years.*
*Starting date should not be **prior** to application submission, as it will imply that the project was started prior to submission.*

11 Invoice reference number: *Both OUS and UiO have electronic ordering systems and centralized invoice receiving (sentral fakturamottak). The purchase order number (PO #) established in your ordering system, or your departments cost center (kostnadssted), MUST be indicated on invoices from any supplier, including MT. As the actual fee from MT can vary, you are advised to enter a cost of 1, - kr in your ordering system. Mattilsynet is a registered supplier at both OUS and UiO. Applicants are advised to write the following under Invoice reference number: "Invoice regarding MT fee must be marked with purchase order number XXXXX".*

Purchase order number must also be included in applications for minor changes in the field "invoice reference".Payment of fees to MT for ethical applications is the responsibility of the applicant.

12 Invoice address: *Invoice address to the project that is to pay for the MT fee.*

OUS Oslo University Hospital Fakturaservice Postboks 4950 Nydalen NO-0424 Oslo fakturaservice@ous-hf.no	**UiO** University of Oslo Regnskapsseksjonen - Sentralt Fakturamottak P.b. 1074 Blindern 0316 Oslo fakturamottak@admin.uio.no

B Public access

Product sensitive details are neither required nor relevant in an ethical application. Generic information on the type and class of test substance is most often sufficient. The sections of the application that is to exempt from Open Files act must be specified – the entire application cannot be exempt.

1 Do the information in the application contain information that should be kept from public access? *Yes/No*

2 If yes, please refer to relevant act(s) and regulation(s) (example: Open files act, article 13, 1st paragraph together with Public administration act, article 13, 1st paragraph, 2nd point): *Enter mentioned paragraphs, if relevant*

3 If yes, which information do you want to keep from public access?
Keep in mind that MT will rarely need sensitive information in their review of and decision on an ethical application. Information related to the type/class of test substance will often be a sufficient and equally relevant substitute for sensitive information. The applicant must specify which parts of the application, including attachments, that is to be kept from public access. The entire application cannot be expected to be exempt from public access. Note that MT will not consider your wish for public access exemption until a demand for public access is raised. If such demand is raised, MT will decide on public access after conferring with the applicant.

C Applicant and participants

All persons involved in planning or conduction of the experiment is to be registered here, Forsøksdyrforskriften cf. article 7, 2. paragraph. Such persons must be added as project participants in FOTS before they can be added as project participants in an application.
Forsøksdyrforskriften requires that all persons planning, conduction and/or participating in animal experiments have sufficient skills and required training within the field and species in question. The rules and regulations regarding animal experimental course was changed by July 1st 2015, when the training requirements in EU directive 2010/63/EU was introduced. The former FELASA category C courses given in Norway is equivalent to a combination of the current categories B and A. The former FELASA category B course is equivalent to the current category A. The CAREIN courses that are now offered at UiO and several other universities in Norway are adapted to the new requirements.

Lab animal course	
Applicant	*Category B, A* and D**
Participant	*Category A and D*
*Supervisor***	*Category B*

** if actively involved/participating in study execution*
*** a category B course is sufficient for supervisors that who is involved in the design and planning of animal experiments, but who will not work with the animals themselves*

All participants that will perform the practical or experimental interventions with the animals must be registered as participants in the FOTS id in question and must be registered with an animal experimentation course that is valid and suitable for their role in the experiment. Only participants with documented category C/BA or B/training (old/new requirements) can be added as participants in a FOTS-id. For registration in KPM's FOTS database as the responsible applicant / participant, KPM's form for new users must be sent with mandatory attachments to the responsible person (PMSK or others) at each section. The form states personal details, affiliation and competence. After KPM has created a FOTS profile, the applicant can send a notification of change in FOTS to add the new employee to one or more projects.
If the lab animal course is prior to July 1st 2015, the signed form on page 12 (reading the new provision to the animal welfare act) of this guiding document must be included in the e-mail. If the lab animal course is non-Norwegian course or a course not conforming to the current or former category designations, please include an official course description and other relevant details (course length (days/hours), lab animal species involved, practical training) with the course certificate.
Personnel that only handle animal cadavers or organs after termination and/or personnel that only assist in data capture (e.g. imaging), without handling live animals, are not considered participants in relation to Forsøksdyrforskriften and are hence not relevant to include in an ethical application.

D Background and purpose

1 Give a short presentation of the background and purpose of the experiment. Describe the hypothesis to be tested. : *It is acceptable and normal that early phase projects often are descriptive and/or explorative by nature, with few or no defined hypothesis. All other projects, and particularly projects describing continuation of ongoing research project, are expected to describe one or more hypothesis that warrant the activity and provide context to the study design and practical performance. Results achieved and their interpretations are relevant to include when applying for continuation of a project, particularly when the need for continued study and the study design are based on such previous results and interpretations. Where relevant, literature references are important to include in the text and as electronic attachments.*

E Research animals

1 Animal species: *Chose the relevant species in the species list provided.*
Provided that the a) phenotypical alterations are comparable (e.g. no clinically observable phenotypic alteration, or phenotypic alterations within the same organ system/physiological function) and b) the severity category caused by the genetic modification and c) possible precautions/efforts are identical, it is recommended to include multiple GM lines on the same page in the FOTS-id. This will greatly simplify annual reporting. All lines MUST be described with relevant designation under "Strain/Line". If the the d) phenotypical alteration are clinically incomparable or e) precautions/efforts and/or f) the categories of severity are not similar, each GM line must be described on separate pages in the FOTS-id.

Note that the Norwegian Directorate of Health approved the KPM animal facilities for enclosed use of GM animals and the combined use of GM microorganisms and animals provided that notification of the use of GM animal lines/combined use ("GMO-melding") are enclosed with every FOTS-id where the animal lines are used. Attachments of relevant "GMO-meldinger"are hence required before applications are send to MT for review. Also note that one "GMO-melding" can include multiple GM lines and that a "GMO-melding" for one or more lines can be reused in subsequent ethical applications, as long as the user, the institution and the responsible person for the facilities listed in the "GMO-melding" are still valid. Please note that it is a copy of the notification that is enclosed in the FOTS application, the responsible applicant must send the notification to the Norwegian Directorate of Health, see procedure in the eHåndbok id 34991.
2 Strain/Line: *All strains/lines are added by relevant and unequivocal designation. If several strains (eg different inbred / outbred conventional strains, or GM strains) with the same severity category) are stated, the reasons for inclusion of the individual strain must be stated in section E16.*
3 Sex: *Both/Male/Female*
4 Number of animals: *If multiple GM lines are included, the total number of animals must reflect all strains and lines on the page in question. The total number of animals must comply with the calculated number of animals needed, including animals in excess of the calculated number (see Calculating number of animals).*
5 Weight at start/finish: *The animals weight/age must be relevant for the described procedures*
6 Age: *The animals weight/age at the start of the experiments must be relevant for the described procedures. The duration must be based on the needs of the experiment and scientific endpoints, not what entails the greatest possible flexibility. Acclimatization, where no procedures occur, does not count as part of the duration of trials.*
7 Number of reused animals (cf. paragraph 17)/Reuse not applicable: *Note that Forsøksdyrforskriften has changed markedly on reuse, requiring special need and arguments for allowing reuse. Note that multiple planned prosedyres does not represent reuse.*
8 Experience with this species: *No/Yes. It is relevant and recommended that the applicant includes the experience of the applicant and all participants when answering this question (provided that the experienced participants actually participate in performing the study)*
9 Duration for the individual animals. State the expected duration of the entire experiment for the individual animal in days, hours, and minutes (e.g. 5, 0, and 0): *It is the maximum duration of the experiment for individual animals that is to be recorded. Assumptions, averages or the time for doing the surgical intervention alone will be erroneous and misleading information. Information about the duration for the individual animal is vital for review of the application, both before and after approval.*
10 Animals with a deviant phenotype: Do the animals have any congenital or hereditary disease/illness or other abnormalities related to their phenotype that may impair their welfare (e.g. diabetes, autoimmune disease, increased tumor incidence, dental defects)? *All animal strains with known hereditary disposition to a deviating phenotype, including animals with genetic defects that do not arise from genetic modification, are to be considered. Note that «No altered phenotype", meaning no clinically observable adverse effects from the genetic modification is the most common presentation of GM animals. This is important to include in the ethical application. If the clinical effects of the altered phenotype depends on the age of the animal, the progression of the alterations and the maximum time that the animals are allowed in the study or to live should be stated. Note that breeding and use of GM lines is subject to application until the applicant has completed an initial Welfare Assessment and documented the absence of a harmful phenotype.*
11 Describe which precautions, efforts and/or treatments the animals will be given in order to safeguard their wellbeing and welfare: Only compensatory measures due to the hereditary / congenital disease / disorder are described here, other measures for refinement are listed under G3. *Actions can range from altering of the diet, altering the routines of monitoring to termination. If the clinical effect*

of the deviant phenotype is dependent upon the age of the animal, the age at which the animals will be used and/or terminated must be defined.
12 Sedation, analgesia and anesthesia: *Anesthesia and analgesia is to be described in terms of active ingredients, concentration, dose (mg/kg or similar), route, frequency and duration of administration. The frequency and duration of analgesia treatment is very important information, frequently lacking. See the comment on multimodal analgesia in section H3. Several variants of common anesthesia mixtures are known in the literature (at least 3 different mixtures containing Zoletil are known). When using mixtures of anesthetic agents, the dosing volume (ml/kg) and the mixing recipe and/or the concentration of active ingredients (mg/ml) must be described. Double check that the anesthesia and analgesia protocol concourse with the description in the Materials and Methods section. It is noted that the use of anesthesia and analgesia is very important information during application review. Information on this topic is quite often incomplete and the applicant is advised to apply appropriate focus on anesthesia and analgesia, and to refer to the text in section E12 of the method description (H2).*
13 Neuromuscular blockers will be used If yes, give further description of the sedation or pain treatment that will be used in connection with such medication: *«Animals must not be administered drugs that abolish the expression of pain unless a suitable anesthesia or analgesia is provided. Scientific documentation of the need and proposed procedure, including details of anesthesia, analgesia and monitoring routines, must be submitted" (§ 14).*
14 Analgesia not applicable *Only tick of this box if the animals are assumed to experience pain, but analgesia is incompatible with the purpose of the experiment. If the experiment is without expected pain, the box should NOT be ticked of.*
15 Rationale for why analgesia can not be used: *Animals that may experience pain at the end of anesthesia must be given pre-emptive and post-operative analgesia as appropriate. If the use of analgesia is incompatible with the scientific purpose of the study, the omission of analgesia in general or classes of analgesics must be described in the application (conf Forsøksdyrforskriften § 14, 4. Led, og Appendix B, 3f). Use of analgesia will affect severity classification! The scientific justification must be stated here.*
16 Rationale for using the chosen animal model: *Confer Forsøksdyrforskriften Appendix A1 - species, strain/line, sex, age, special traits, genetic modifications*

F Calculating number of animals

1 Describe the rationale and justification for the number of animals that will be used. Pilot experiments must be performed in case of uncertain population size, confer Forskriftens § 6, 2. ledd. Seek statistical help if you are in doubt. *If uncertain about population size or severity, pilot experiments shall be carried out, cf. Forsøksdyrforskriftens § 6, 2nd paragraph. Seek help from a statistician if in doubt.* *The justification and prospective calculations on the required number of animals is often insufficient or missing. Describing the statistical methods that is intended to be applied on the obtained results is a misunderstanding – calculating the number of animals is a prospective analysis. Delayed processing of the ethical application is likely if animal numbers are not justified by prospective calculations. If insufficient data are available for prospective statistical analysis, a logical estimate or a pilot study is required. If (pilot-) studies with the same or similar animal models are previously performed, existing study results are expected to be used for prospective calculation of required number of animals.*

Calculating the number of animals in breeding projects can obviously be difficult. The input that the applicant has used in his/her estimation (fertility, genetics and how it affects the number of offspring with the desired genotype and number of offspring required for experiments, analysis or colony maintenance) must be included. Calculating the number of animals in a breeding project is otherwise considered to be an estimate. NB - an estimate does not imply that an "open end" number of animals can be used – it just implies that the allowed maximum number of animals was derived by estimation. The breeding protocol represents a deviation from the use of research animals in in vivo experiments, where the prospective calculation of the required number of animals is expected with a higher degree of precision. Be aware that breeding of GM lines requires a FOTS application, unless an initial welfare assessment has documented the absence of a harmful phenotype. *In some experiments (e.g. surgical interventions, post mortem processing of organs), a certain degree of surgical failure or data loss is expected when the operated animal or organ does not comply with defined inclusion criteria. A certain number of extra animals, in addition to the calculated number of animals, will hence be needed to compensate for used but excluded animals. It is acceptable to apply for extra animals, in addition to the calculated number, provided that the extra animals are justified and reasonable and that this is written explicit in the application. Do not describe the need for 100 animals and apply for 110 without explaining why an extra 10 animals are needed.*
2 Describe all experimental groups and group sizes. Attach a table when needed *Note that tables copied directly into FOTS and table-like organization of data directly in FOTS becomes chaotic nonsense in a print-out. Tables are often very illustrative, but include Word- or Excel tables as Attachments.*
3 Describe the statistical method used to determine the number of animals. If statistics can not be applied, describe why.

G Alternatives/3R

Alternative, scientifically relevant methods not involving the use of animals should always be considered. Review relevant alternative methods and why these are rejected, considering the 3Rs ("Replacement, Reduction, Refinement").

1 Replacement: Why is it not possible to achieve the aim of this experiment without the use of animals? What alternatives have been considered and why were they rejected? *Replacement is obviously not available or relevant in some select cases. However, "Not relevant" is not a relevant fulfillment of the legal requirements to review alternatives. Formally speaking, alternatives are in many cases available, but they are most often not relevant. Your conclusion on suitability of alternatives can only be reviewed by MT if the nature of the alternative methods has been described. To fulfill the legal requirements and enabling MT and others to review the alternatives AND your conclusion on suitability, the alternatives must be presented as objectively and in depth as possible. Conclude with the up- and downsides of the available alternatives versus the applied use of research animals. It is insufficient for applicant to merely present his/her conclusion about little described alternatives.*
2 Reduction: When the use of animals is unavoidable: What has been done to minimize the number of animals and still achieve valid scientific results? *The most important measure will be a logic and transparent prospective calculation of animals needed. Critical review of how and when control animals are used could also be relevant (control animals are often included several times).*
3 What measures have been planned to optimise the wellbeing and welfare of the animals? (Keywords: analgesia, anesthesia, endpoints, environmental enrichment, surgical techniques, sampling techniques etc.) *Experience from prior (pilot) experiments or literature must be used to reduce and refine future protocols and ethical applications.*

H Methods description

When writing ethical applications and performing animal experiments, one simple rule applies: ***Write what you do and do what you write***. The description of you ethical application must enable MT to assess the technical performance of the experiment, how this will affect the animals and the obtained results and how the study will meet the described study objective. The technical performance of the experiment must be described in a clear and complementary text, enabling an objective assessment of study performance versus the ethical application by designated persons at KPM. It is recommended to include a coherent logic description of all planned procedures in chronological order in one of the text boxes, rather than answering the questions in all text boxes with short and incoherent answers. The later often leaves the reader with little or no insight into the flow, timeline and bigger picture of the project.

1 Preparation of the animals before the actual laboratory experiment.
Describe any purchase, transport, quarantine/acclimation, housing, environmental enrichment, feeding regime:
Training/preparing of the animals prior to study start? Use of metabolism cages or other type of physical restraint or reduced freedom of movement? Use of equipment that requires an activity that is not voluntary and/or normal (e.g. running on a treadmill)? Training and accommodation of the animals prior to study start should be described where relevant.
Note that cage groups should not be reorganized after acclimatization and the number of animals per cage should therefore be considered carefully when setting up the study plan.

2 Which procedures will be applied to each animal during the experiment (e.g. tracking, capture, restraint, handling, tagging, transport, anesthesia, surgery, administering of test substance, and more)? Describe the procedures as regards method, duration, and frequency. For blood samples the volume and method must be described. For injections include location, method administering, and volume to be administered. Describe incarceration/immobilisation necessary to perform the procedure.

- *Method of ID marking and biopsy sampling must always be described, also if traditional ear tagging is used. Note that a method of biopsy that also results in ID marking must be the default method applied at KPM (see guideline for biopsy and ID marking of rodents).*
- *Remember to add ALL test substances, drugs and chemicals that the animals will be exposed to. Administration of test substances that are not described in an approved FOTS-id represents noncompliance with regulations and OUS procedures. Dose levels (mg/kg) are always relevant, but dosing volume and route of administration is equally important (and often omitted) information.*
- *The provision has a general requirement for anesthesia when performing procedures on research animals. However, anesthesia can be omitted if anesthesia is considered more stressfull than the procedure itself, or anesthesia is considered to be incompatible with the study purpose. Literature clearly document that physical restraint is very stressful for rodents, and often more so than minor rapid procedures. Only routine procedures, that can be completed rapidly by skilled technique and require short periods of physical restraint, can be performed under physical restraint only. Physiological effects of anesthesia induction, including physical restraint/handling, are marked. The use of anesthesia should hence be considered carefully and simple minimally invasive procedures that can be performed rapidly with correct technique should not be performed by applying anesthesia. Routine SC/IP injection and standard blood sampling in rodents are examples of procedures that are performed best without anesthesia. When physical restraint or anesthesia will be used for sampling, injection and/or other procedures, describe the number and duration of (repeated) procedures, anesthesia and physical restraints that is planned.*

- *Even if described in the Research animal section, it is recommended to refer to the use of anesthesia and analgesia as described in section E12, to get a complete understading of anesthesia, analgesia, observation time after conclusion of the surgical intervention and supportive therapy (heat, fluids, other) in context with the experimental procedures.. Anesthesia and analgesia are central elements in the cost-benefit analysis evaluation of severity category. It is also one of the topics that most often give rise to questions and requests for change. The applicant is hence adviced to choose an anesthesia that is fit for purpose include a complete and complementary description. Multimodal analgesia, which is combining opioids, local analgesia and NSAIDs, provides additive effects and is the expected standard analgesia. If the nature of the procedures or the study purpose indicate that only 1 or 2 of these drug classes can be used. The applicant must warrant why the expected standard multimodal analgesia cannot or should not be used.*

- *Describe experimental groups, preferably with an attached table. A table (provided as attachment) that provides an overview of experimental groups, dose levels, dosing and sampling interval and observation time will provide clarity. Describing the experimental groups and above information as text only will create little clarity and cannot be recommended. Note that animals dosed with different dose levels or identities of test substances should not be housed in the same cage after dosing.*
- *Technical description of*
  -surgical interventions, incl. timing, if more than one intervention are planned
  -injections
  -sampling of blood, including methodology and details related to volume per sampling, number of samples and frequency of sampling.
  -sampling of other tissues than blood (including organs at or after termination).
  -frequency, duration and the total number of anesthesia procedures when performing imaging (UL, CT, MR)
- *Ethical applications with surgical interventions as central elements are often missing information on other procedures that are planned. It is important to include ALL activities and procedures in the Methodology description (e.g. behavior studies, special diets etc.), not just surgery.*
- *Details regarding dosing volume and dose of active substance per dosing, number of dosages, route of administration and speed of injection (ml/min by IV injections). Assumed clinical effects at the chosen dose levels should be stated when the test substances are likely to cause adverse or toxic reactions.*
- *Attachments may supplement and expand the information supplied, but should not be a substitute for submitting a complementary text in the ethical application form.*

3 Make a description of the experiment's design, and pinpoint any experimental endpoints. You are encouraged to include an illustration displaying what will be done to the animals or groups of animals at what time (timeline). *The data sampled will set the study purpose in context. Experimental or scientific endpoints are the time when the necessary amounts of data that were planned to be collected (to state the purpose of the experiment and to clarify the underlying hypothesis) are available. The duration of trials cannot continue beyond defined experimental endpoints.*

4 Describe the follow-up and supervision of the welfare of the animals during the experiment (before, during, and after procedures). *Describe possible and expected adverse effects. When relevant, a plan for monitoring must be described, detailing monitoring frequency at critical periods and planned actions. The provision requires minimum 1 daily inspection of the animals and <u>more</u> than 1 inspection per day may be required at critical periods of an experiment. Planned actions are often described very briefly, or not at all. In experiments classified as moderate, a plan for monitoring and action (i.e. score sheet) <u>may</u> be relevant to include if markedly reduced condition or marked body weight loss (above 15%) is <u>expected</u>. In experiments classified as severe, a plan for monitoring and action (i.e. score sheet) <u>must</u> be included. The score sheet must include clinical parameters that are*

relevant for the expected adverse effects. A general type of score sheet is available as an example on the KPM web-page. Score sheets should not be included when markedly reduced condition or marked body weight loss are not expected (i.e. all non-recovery and mild severity score experiments, some moderate severity score experiments).

5 If animals are to be euthanized:
Which method of euthanasia will be used (cf. regulations § 16, part 2 and appendix C)? *Cervical dislocation should always be the preferred method for mice euthanasia, unless there is a scientific / methodological justification for other euthanasia methods. Euthanasia using CO_2 causes considerable stress and euthanasia with CO_2 should therefore follow OUS procedure 132099. For mice this means that CO_2 can be used when performing euthanasia on 8 or more mice. Any deviations from the described animal numbers must be scientifically justified in an approved application.*
Note that approved methods of killing animals (including requirements) are described in Vedlegg C to the provisions. Any method of killing that deviates from those described in Vedlegg C must be explicitly described in the ethical application and approved prior to use. The description must include a scientific rationale for the choice of method and why the methods in Vedlegg C cannot be used. When animals are killed by an anesthetic overdose, active ingredient and dose level must be stated. Note that KCl is not included in Vedlegg C and that decapitation can only be used if "other methods are not possible". In reality, this means that the choice to kill animals by decapitation requires a scientific rationale (e.g. harvest of brain or brain stem).
Killing of rodents, rabbits and neonate dogs by concussive/ percussive blow to the head and killing rabbits by electrical stunning is described as approved methods in Vedlegg C. These methods of killing animals are grossly inappropriate and are absolutely NOT approved as method of killing at Oslo University Hospital.

6 If a method of euthanasia will be used, that is not mentioned in appendix C:
Describe and give a reason for the chosen method of euthanasia (cf. regulations § 16).

7 Criteria for humane endpoints, i.e. setting of clear, predictable and irreversible criteria that allow early termination of the experiments before the animals experience significant harm whilst still meeting the experimental objectives. An adapted score form may be attached to the application.
Humane endpoint, i.e. clinical symptoms that indicate serious and unnecessarily severe strain and/or impending death, must be pre-defined and as specific as possible. Subjective and little specific HE are very often seen and give no guidance on interpretation and action. "The animals will be killed if the suffer unnecessarily «is an example of a meaningless HE.
Humane end points are also relevant in non-recovery experiments (e.g. inability to maintain the animal in stable surgical depth anesthesia) and breeding experiments (deviations from normal clinical state/physiology). Unless the breeding animals are rare and truly unique animals, the tolerance for deviating clinical status will be very limited. "Not applicable" is therefore not an option for HE.

8 Which actions will be taken if animals reach the humane endpoint (examples: treatment of symptoms, reduced exposure or euthanasia)? *Therapy by analgesia, antibiotics or killing is typical actions. If actions other than killing are planned, more frequent monitoring must be part of the plan. Monitoring in itself is not an action. The described measures must be linked to the human endpoints, ie different endpoints may have different measures.*

I Attachments to the ethical application

The provisions to the law on genetically modified organisms and the law on environment, health and safety requires that GMO notifications and HSE risk evaluations are included in all ethical applications where these are relevant. The Ministry of Health also requires that KPM keeps a record of all activity that include GMO and that ethical applications are only approved if valid GMO notifications are included

When relevant, following attachments is mandatory prior to sending an application to MT:

-A copy of a valid GMO notification (Arbeid med genmodifiserte organismer (GMO) ved Komparativ medisin)
-HSE risk evaluation form (Bruk av kjemikalier i forsøk –KPM)
-Test result for cell lines (Import og in vivo bruk av biologisk material-KPM)*

Applications are returned to the applicant if relevant attachments are missing. These demands are independent of the Regulation on Animal Experimentation.

*KPM accepts that test results is presented after submitting the application, if the results are not yet available at the time of application. Be aware that a cell line can not be imported to KPM before the section leader at the given KPM section has approved the import. The test result is to be submitted to the PMSK at the current section as soon as possible to avoid project delays.

Applying for change in previously approved FOTS id

Any change of an approved project that may have a negative impact on animal welfare must be applied for and approved by MT, conf Forsøksdyrforskriften § 6. Changes that are considered to have no negative impact on animal welfare require notification only. FOTS has 2 options; Application for minor changes and Notification of change. When minor changes of previously approved FOTS id are needed, the applicant must describe 1) Purpose of the change, 2) the required changes and how the required changes will affect animal welfare in either "Application for minor changes" or "Notification of change". **Remember to include PO No (exception: application for change to extend a projects duration) duration**

PMSK decides if a project change must be applied or notified to MT and document their decision in the FOTS-id. The applicant submits notification or application to MT according to these instructions

Guiding document on typical changes

Change	Assessment	Comment
Extension of project end date	Application	Extending the project end date has no negative effect on animal welfare. However, changing the end date of an approved project requires an authority that only MT has. Note that the project period and the maximum length of the procedures for individual animals are 2 separate issues.
Expanded animal numbers	Application	Expanding the animal numbers will have an overall negative effect on animal welfare.
Altered composition of animal lines and genotypes within same species. No change in total animal numbers within species in question	Notification	If the desired change is a relative change between different animal lines, with or without altered phenotype, and the previously described severity classification is not altered.
	Application	If the desired change will increase the number of animals in a higher versus a lower severity category compared to the original application.
Altered anesthesia/analgesia	Most often notification	Notification requires that the qualitative effects of the altered anesthesia and analgesia remains as previously described.
Including new participant/altering responsible applicant	Notification	Requires that the participant/applicant can document the required competence and education, and is registered in FOTS. The applicant is responsible for submitting required information to PMSK
Including new test substance	Variable	Assumed/known effects of the intended new test substance versus the previously approved test substance(s) are essential. Notification is only an option if similar test substances were included in the original FOTS id and the identity and effects of the new test substance can be considered to be comparable to the test substances or family of test substances previously approved.

Ny forsøksdyrforskrift ble vedtatt med virkning fra 1/7-2015.

Alle brukere av KPM og PF som er eller ønsker å bli registrert som forsøksansvarlig eller medarbeider i FOTS, og som har gjennomført forsøksdyrkurs *FØR* 1/7-2015, skal dokumentere at de har vedlikeholdt sin kompetanse og har lest den nye forskriften. Signert dokument skal returneres til KPM/PF som elektronisk PDF-kopi.

Undertegnede signerer hermed for å ha lest **Forskrift om bruk av dyr i forsøk** (FOR-2015-06-18-761)[1].

Navn i blokkbokstaver: _____

_____ _____

Dato Signatur

The new provisions to the animal welfare act has been in effect since 1/7-2015.

All KPM and PF users that are or wants to be registered in FOTS as responsible applicant or participant, and have completed their lab animal course *BEFORE* 1/7-2015, must document that they have maintained their competence and read the new provisions to the animal welfare act. The signed document must be returned to KPM/PF as an electronic PDF copy.

I, the undersigned, have read **Forskrift om bruk av dyr i forsøk** (FOR-2015-06-18-761)[1].

Name in capital letters: _____

_____ _____

Date Signature

[1] Den nye forskrift er tilgjengelig på Lovdata.no (https://lovdata.no/dokument/SF/forskrift/2015-06-18-761).
The new provisions to the animal welfare act is available at Lovdata.no (https://lovdata.no/dokument/SF/forskrift/2015-06-18-761)

Lokal vurdering av forsøksdyrsøknader ved Oslo Universitetssykehus[2]

FOTS id: **Forsøksansvarlig:**

A. Prosjektet er teknisk, praktisk og ressursmessig gjennomførbart ved forsøksdyravdeling:
☐ Ja ☐ Nei Kommentar: _____

B. Fakturaadresse er anført: ☐ Ja ☐ Nei **Bestillingsnr anført**: ☐ Ja ☐ Nei ☐ Ikke relevant

C. Søknaden inneholder nødvendige formelle opplysninger (Forsøksdyrforskriftens vedlegg A og B)

Formelle opplysninger	**Ja**	**Nei**
Den foreslåtte klassifiseringen av forsøkene etter forventet belastningsgrad, jf. Vedlegg B	☐	☐
Kompetanse hos de personene som deltar i forsøket	☐	☐
Gjentatt bruk av dyr og den samlede virkning av dette på dyret	☐	☐
Planlagt bruk av bedøvelse, smertestillende midler og andre former for smertelindring	☐	☐
Forsøks- eller observasjonsstrategi, statistisk design for å minimalisere antallet dyr, smerte, frykt og annen belastning, der det er relevant	☐	☐
Bruk av metoder for å erstatte, redusere og forbedre bruken av dyr i forsøkene	☐	☐
Tiltak for å begrense, unngå og lindre enhver form for belastning for dyrene, fra fødsel til død, når det er relevant	☐	☐
Tiltak for å unngå unødvendig gjentagelse av forsøk, når det er relevant	☐	☐
De forholdene som dyrene oppstalles, holdes og stelles under	☐	☐
Avlivingsmetoder	☐	☐
Bruk av humane endepunkter	☐	☐
Relevansen og berettigelsen av a) bruk av dyr, inkludert deres opprinnelse, anslåtte antall, art og livsstadier b) forsøkene	☐	☐

Kommentarer: _____

[2] Vurdering skjer iht Prosedyre for forsøk med dyr ved Oslo Universitetssykehus HF, dokument-ID 83692.
Ved mangler vil søknaden settes i kladd, og søker informeres i en egen mail om at søknaden ikke sendes til MT før alle mangler er adressert. Om søker ved andre gangs og senere innsending ikke har adressert manglene på en adekvat måte, settes søknaden tilbake i kladd.

D. Den tekniske gjennomføring, forventede kliniske effekter og tiltak er beskrevet utfyllende og klart

Aktivitet	Ja	Nei	Aktivitet	Ja	Nei
Humane endepunkter, inkl evt scoreskjema, og tiltak	☐	☐	Annen oppfølging og overvåking av negative effekter på dyrene	☐	☐
Tekniske prosedyrer, inkl metode, rute, frekvens og det totale antall av injeksjoner/prøveuttak/prosedyrer	☐	☐	Avvikende fenotype og kompenserende tiltak er beskrevet	☐	☐
Volumen, frekvens og det totale antall av injeksjoner og blodprøver	☐	☐	Varigheten av forsøket for det enkelte dyr	☐	☐
Anestesimetode og – dose	☐	☐	ID-merking og uttak av biopsi	☐	☐
Analgesi, inkl frekvens og varighet	☐	☐	Metode for avliving	☐	☐
Understøttende tiltak etter prosedyre	☐	☐			

Kommentarer: _____

E. Vurdering av søknaden i fht GMO- og arbeidsmiljøforskriften*, og vurdering i fht KPMs krav til import av cellelinjer:

Informasjon	Ja	Nei	Ikke relevant
Melding om innesluttet bruk av GM dyr/GMO	☐	☐	☐
Prosjekttillegg om HMS-aspekter	☐	☐	☐
Sikkerhetsdatablad	☐	☐	☐
Det skal benyttes cellelinjer i forsøket. Søker er forpliktet til å dokumentere fravær av uønskede smittsomme agens før import til KPM, jf OUS prosedyre 114241 Import og in vivo bruk av biologisk materiale	☐	☐	☐

Kommentarer: _____

*Begge forskrifter og H-direktoratets godkjenninger av forsøksdyrlokalene for innesluttet bruk av GMO legger til grunn at forsøksdyrsøknader ikke skal godkjennes før relevante meldinger og risikovurderinger er inkludert i søknaden. KPM har ansvaret for at disse forskrifter overholdes, uavhengig av Forsøksdyrforskriften. Søknader returneres derfor til bruker for oppdatering dersom vedlegg mangler.

Dato søknad sendt: _____

Ansvarlig person ved avd KPM/PF: _____

Dato: _____ [3]

[3] Denne lokale vurdering lastes opp som vedlegg til aktuell FOTS id, til informasjon for søker og MT. Vurderingen gjelder FOTS id sendt aktuell dato. Ved revisjon av søknaden kan vurderingene være uten relevans for endelig versjon av søknaden. Dette forutsettes avklart av MT ved versjonskontroll av aktuell FOTS id. Vurderingen er å betrakte som elektronisk signert av anførte ansvarlige person ved opplasting i FOTS.

Lokal vurdering av endringsmeldinger og endringssøknader ved OUS[4]

FOTS id: **Forsøksansvarlig:** ☐ **Melding om endring** ☐ **Søknad om endring**

Effekt på dyrevelferden

☐ Søker kan sende melding om endring.
Den omsøkte endringen vurderes ikke å ha noen negativ effekt på dyrevelferden.

☐ Søker må sende søknad om endring.
Den omsøkte endringen vurderes å ha negativ effekt på dyrevelferden og/eller må saksbehandles av MT.

Søknaden inneholder nødvendige formelle opplysninger	**Ja**	**Nei**	**Ikke relevant**
Formål og hensikt med endringen	☐	☐	☐
Metodebeskrivelse	☐	☐	☐
Gruppestørrelser	☐	☐	☐
Ny medarbeider er registrert i KPMs FOTS-database Hvis det er krysset av for nei: *Send epost til seksjonsleder ved aktuell seksjon med informasjon om ny medarbeider: navn, mobilnr, epost, høyeste fullførte utdannelse, kursbevis (pdf). Melding sendes først fra KPM til MT når medarbeider er korrekt registrert.*	☐	☐	☐
Oppdatert prosjektsammendrag	☐	☐	☐
Redegjørelse for hvorfor endringen ikke svekker dyrevelferden (endringsmeldinger)	☐	☐	☐
Bestillingsnummer er lagt inn i feltet fakturareferanse (endringssøknader)	☐	☐	☐
Vedlegg: Melding om innesluttet bruk av GM dyr/GMO	☐	☐	☐
Vedlegg: KPM prosjekttillegg om HMS-aspekter	☐	☐	☐
Vedlegg: Sikkerhetsdatablad	☐	☐	☐
Det skal benyttes cellelinjer i forsøket. Søker er forpliktet til å dokumentere fravær av uønskede smittsomme agens før import til KPM, jf. OUS prosedyre 114241 Import og in vivo bruk av biologisk materiale	☐	☐	☐

Kommentarer:

Dato melding/søknad sendt: _____

Vurdering gitt av ansvarlig person ved KPM-OUS: _____

Dato: _____

[4] Vurdering skjer iht Prosedyre for forsøk med dyr ved Oslo Universitetssykehus HF (dokument-ID 83692), Forskrift om bruk av dyr i forsøk, Forskrift om innesluttet bruk av genmodifiserte dyr, Forskrift om innesluttet bruk av genmodifiserte mikroorganismer, Arbeidsplassforskriften og Prosedyre for import og in vivo bruk av biologisk materiale ved KPM (dokument-ID 114241).
Dersom nødvendige formelle opplysninger eller vedlegg mangler, settes endringsmeldingen/endringssøknaden i kladd. Søker informeres per e-post, slik at manglene kan korrigeres og endringen sendes inn på nytt. Søknaden sendes til Mattilsynet når alle manglene er adressert.