Practical guidance for applying for animal experiments in FOTS

All applicants are expected to consult and actively use this guidance document when writing FOTS-applications.

Submitted FOTS-applications that lack much of the essential information described in this guide, will be returned to the applicant without any further comment than to consult the guide.

Content

Background and scope

This guidance document has been compiled to advice applicants on how to apply for experiments in the Norwegian electronic system for animal research – FOTS. The guide is based on the current legislative demands, the requirements and recommendations published by Mattilsynet and on the experience of PMSK of common short-comings and errors in submitted applications.

The legal requirements for applications for animal experiments can be found in the Norwegian Regulation on animal experimentation which to a large degree is concurrent with the EU Directive for animal research (Directive 2010/63/EU).

The competent authority for animal research in Norway is the **Norwegian Food Safety Authority (Mattilsynet)**

Applicants can find guidance information on applications at Mattilsynet (in Norwegian only):

Søke om godkjenning for å bruke dyr i forsøk | Mattilsynet

Access to FOTS: User account, login and language

Contact PMSK by email to obatin username/password to FOTS.

The following information is needed in order to be registered in FOTS:

1. Full name, E-mail adress and Phone
2. Academic degreee
3. Documentation of required **theoretical training** according to the legal requirments (EU Commission Education and Training Framework, e.g. EU function A and B for those who will plan and perform procedures on animals
4. Documentaiton of **practical skills** as required by legislation (EU Commission Education and Training Framework)
5. Documentation of **CPD (continous updating of competence)** as required by the legislation (EU Commission Education and Training Framework) if it is more than 5 years since completed animal research course.

NOTE: If the animal research course is not a Norwegian course and not accredited by FELASA, please include an official course description and other relevant details (course length (days/hours), lab animal species involved, practical training) with the course certificate. All documents must be in Norwegian or English and only officially translated document will be accepted.

Login: FOTS can be accessed here: https://asp.gitek.no/fdu/pmws.dll/Login .

Language: An English version of FOTS can be chosen before log-in by clicking the English flag. The application has to be written either in Norwegian or English.

NOTE: Out of courtesy to those who will read and assess the application and for efficient application processing, the application should be written *either* in Norwegian or English. Avoid switching between languages in different parts of the application. This makes it difficult to read.

Confirmation regarding animal facility

Applicants are advised to contact the manager of the topical animal facility at NMBU at an early stage of the planning process. Factors that should be discussed and agreed on include, but are not limited to: ability, capacity, economy, necessary infrastructure and resources (including personnel) that will be needed to carry out the planned experiment.

When performing the experiments at one of NMBUs approved animal facilities, the form "Confirmation animal facility" which you find as attachment 1 to this guide must be signed by the applicant **and attached to the FOTS-application**

.

NOTE:

- The confirmation form does not release the applicant from responsibility to maintain close dialogue with the animal facility in further planning and execution of the experiment
- The veterinary clinics are not approved animal facilities (experiments in the clinics are field experiments)
- The confirmation form requires you to provide the FOTS ID, *so the form can only be signed after you have created, but not submitted,* the new FOTS-application.
- Experiments conducted on animals in *another* institution than NMBU must be submitted in FOTS via the topical institution (*not* via NMBU). Contact the PMSK at this other institution to get access in FOTS to the correct animal facility
- In a few exceptional cases it might be topical that animals will be shipped from an animal facility at NMBU to another institution during the experiment. Contact the PMSK at NMBU for advice in such cases

Rules of procedure for FOTS applications

Local review of FOTS applications prior to submision to Mattilsynet

Mattilsynet requires that all applications are quality controlled locally by the the named animal care and welfare officer (= Person med særskilt kontrollansvar, **PMSK**) at the institution before applications are submitted to Mattilsynet.

Upon submission of a FOTS-application by the applicant, the application first goes to local review at PMSK.

The FOTS-application *is NOT send automatically to the authority (Mattilsynet).*

The application is reviewed by PMSK, and is then either forwarded to Mattilsynet *or* reset to "DRAFT" in FOTS and send back to the applicant for revision if it has short-coming and is regarded as incomplete. The processing time for the local assessment by PMSK depend on the number of applications in the pipeline and can vary between 1-3 weeks.

Only applications that fulfil the legal and formal requirements will be forwarded by PMSK to Mattilsynet for processing.

Non-technical public summary

Certain fields in the FOTS-application are marked with a globe. Fields marked with a globe will be collected into a public summary which will be published at **Mattilsynet's web page** and in the **EU Commission ALURES database for non-technical summaries.**

Each field marked with a globe in the FOTS-application, has a text limit of 2,500 characters.

Fields marked with a globe must not contain confidential or personal information!

The public summary should be regarded as the researcher's opportunity to inform the public on the need for animal research, its expected benefits, how harms are reduced to a minimum, and how the expected benefits outweigh the expected harms to the animals.

Transparency and public right of access to FOTS applications

When an application is submitted to Mattilsynet via FOTS, it is automatically registered in the Norwegian official database for the public sector, Einnsyn

In the Einnsyn register, the FOTS ID, title and name of insitution is provided, see an example here: eInnsyn - Case: 2021/75510 - Norwegian Food Safety Authority

In our experience animal welfare organizations regularly ask for access to FOTS applications (in any stage of the process *after submission to Mattilsynet*). In addition, we also experience that journalists may ask for access.

Anyone from the public has the right to search for and order access to the documents published in eInnsyn. Unless the FOTS application and/or related documents in the case contain confidential information, it will be released in full at any stage of the application process after it has been submitted to Mattilsynet.

NOTE:

- Applications that have the status of "DRAFT" or is submitted to "LOCAL REVIEW" in FOTS **is not** available for anyone else than the applicant, the co-workers listed in the application, and PMSKs.

- It is possible to **withhold confidential information**, please see further information in the STEP-by-STEP guide later in this document

Application assesment by Mattilsynet (including handling time)

The general requirements for FOTS-applications can be found in Chapter III and Annex A in the Norwegian regulation on animal research. Further requirements for the assessment made by Mattilsynet can be found in Chapter 3 in the Instruks for Mattilsynets forvaltning av forsøksdyrforskriften

The processing time in Mattilsynet can be up to 40 *working* days (+ 15 days for especially complicated applications).

When submitting a FOTS-application, the start-date cannot be set earlier than 12 weeks after submission date (to take into account local review and Mattilsynet´s processing time)

Mattilsynet can decide to use **external experts** to review the application. Mattilsynet can also contact the applicant for **supplementary information**.

Applicants are responsible to take into account the handling time of Mattilsynet and local review when applying for animal experiments, se further information under "Planned start date" in the STEP-by-STEP guide

Any requests to Mattilsynet concerning FOTS-applications should should be discussed with PMSK first, and PMSK must be included in all communiation with Mattilsynet

Fee for application handling

Mattilsynet charges fees for handling of applications. The current fees (as of 2023) are as follows:

Category*	***Type of application***	***Fee (NOK)***	***Comment***
B	Application for change in a current FOTS application	1700,00	If the application only regards extension of the approval date, fee is *not* charged.
C	Application for pilot study	4250,00	
D	New FOTS appliation	6800,00	Mattilsynet can decide that this fee can be reduced to category C for *"thoroughly prepared and non-complex applications"*

** The categories are defined in the "Regulation on fees for defined services of Mattilsynet"*

THE APPLICATION FORM IN FOTS – STEP BY STEP

The tables on the following pages, follows the heading titles and format found in the online FOTS-form and provides guidance and advices based on the legal requirements as well as some tips and advice for typical "pit-falls.

Tabeles or tabulated text that are copied/made in the online FOTS-form becomes unreadable nonsense in the pdf-file that is generated of the application form when the application is submitted. Tables may be very useful, but **tables and figures have to be *uploaded as attachments* in FOTS** and not included in the text field in the electronic application form.

Language: Applicants can decide to write the application in Norwegian or English. For efficient application processing, the application should be written *either* in Norwegian or English. Avoid switching between languages in different parts of the application. This makes it difficult to read.

The field marked in RED and with a globe in the table below will be included in the public non-technical summary that will be published in the European Commission ALURES database. **The fields marked with a globe must not contain any confidential informaiton nor information that can identify persons or institutions!**

General information

Working title: Provide a short and descriptive title for the project (use same language, e.g. Norwegian and English consistently troughout the application)
International ID: ID in the EU's Public summary database ALURES. The number is *generated automatically*, not to be filled in by the user.
Establishment where the experiment/project will be conducted: NMBU has 4 registered establishments/units in FOTS. These are: • **101 NMBU Sandnes**: for experiments to be conducted at the veterinary facility in Sandnes, Rogaland • **109 NMBU Fiskeforsøk**: for all experiments involving fish and other aquatic animals (except marine mammals). Includes both model fish, aquaculture fish and wild fish and experiments conducted at fish facilities at NMBU and field experiments.

- **170 NMBU Laboratoriedyr:** for all experiments involving rodents and rabbits.
- **174 NMBU Produksjonsdyr, sports-og familiedyr, feltforsøk:** for all experiments involving production animals, companion animals, and field research. This include experiments that will take place in approved animal facilities at NMBU (such as SFH, the infection unit for production animals at Eksbio VET, the Metabolism unit), as well as field trials in the veterinary faculty clinics, in private veterinary clinics, field experiments in livestock herds, as well as field experiments on all wildlife species other than fish

NOTE: If you are a user of several of NMBUs facility, please make sure to select the correct NMBU unit appropriate for your experiment.

Application category

Two possibilities, either “Pilot experiment” or “New Experiment”. Select the appropriate category.

The Norwegian regulation on animal research §6 requires a pilot study *if the methods are new with unknown effects on the animals and/or if there is uncertainty on how many animals that are needed for the study*

Keywords:

The purpose of the keywords is to be searchable terms in the EU Alures database of public summaries.

Enter keywords that are clear, specific, and informative. **Neither animal species nor purpose of the study** should be listed as keywords (as these are generated into the public summary from other fields of the FOTS-application).

You can either choose keywords from the available list or create new keywords. You can provide up to 5 keywords.

Other

Field experiment, including localization and scientific justification: Experiments outside approved facilities.

As a general rule according to §12 in the Norwegian Regulation on animal research **all experiments should be conducted in an approved animal facility. Mattilsynet can grant exemption from this requirement if it is scientific justified that the experiment is conducted outside an approved facility.**

- According to the legislation all field experiments are exemptions
- Field experiment = all experiments conducted outside an approved animal facility

NOTE: Field experiment is not only experiment involving wild animals. For example, an experiment carried out in a commercial fish farm will be regarded a field experiment. Similarly, an experiment carried out at a veterinary clinic (NMBU or others) is a field experiment.

Multiple generic projects (“blokkforsøk”) cf. Norwegian regulation §6, part 5,

This refers to special projects most performed within industrial/commercial diagnostic/toxicology/pharmacology. **Usually not relevant at NMBU**. Contact PMSK if you are in doubt.

Previous experience with comparable procedures (YES/NO)

It is relevant and recommended that the applicant includes the experience of the applicant and all listed co-workers when answering this question

NOTE: it is required that **all co-workers that contribute to planning or performing animal experimetns must fullfill the requirements for competence and be listed in FOTS.**

Experiments/procedures funded by

Choose the most suiable option in the drop-down-menu are:
“Annen finansieringskilde” = Other finance source
“Den norske kreftforening” = The Norwegian cancer association
“EU/EØS midler” = EU/EEA (European Economic Area) funding
“Forskningsrådet” = The Norwegian Research Council
“På oppdrag fra offentlig etat” = Commisioned by a public agency
“På oppdrag fra privat bedrift” = Commisioned by a private company

NOTE: All applications are expected to hold the same quality irrespective of funding source. Applications supported by large and important funding institutions (like EU and/or Forskningsrådet) obviously is an indicator of relevance and high scientific quality, but it is important to realize that funding from these sources does not consitute an ethical approval to perform animal experiments. Consequently, **all applications are expected to contain the same level of detail and be complete, irrespective of funding source.**

Planned start and end date

START DATE:

Start-date cannot be set any earlier than minimum 12 weeks after submission date

Applicants must take into consideration the time for local review by PMSK and the handling time at Mattilsynet.

NOTE: The 40 (+15) days handling time at Mattilsynet, is **working days** meaning that handling time may increase in periods with holidays.

Start date must not be prior to application submission, as it will imply that the project was started prior to approval. Take into consideration both local review of application (1-3 weeks) and Mattilsynet´s handling time (up to 40 working days) when setting the start date.

NOTE: **Ceck start-date before submission, and also after any revision of the application**

NOTE: **Animals must not be bred, purchased, or in any way be prepared for experiments before the FOTS-application has been approved by Mattilsynet**

END DATE:

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 will be invoiced by Mattilsynet.

Applications for experiments performed in an approved animal facility can be approved for up to 4 years and it is advicable to take advantage of the full availbe project approval period.

The following facilities are approved facilities at NMBU:

- **For fish research**
  - Fiskelaboratoriet
  - Salmon infection unit VET
  - Model fish unit VET
  - Isotope laboratorium
  - FIGARO Gamma/UV facility
- **For laboratory animals**
  - Rodent facility VET NMBU
  - Mice facility BIOVIT
- **For production animals**
  - SHF
  - Metabolism unit
  - Eksbio production animal unit VET

NOTE: The veterinary clinics for small and large animals are NOT approved research animal facilities. Experiments conducted in the clinics are field experiments.

Field experiments can be approved for up to 2 years.

Invoice information (reference number and invoice adress)

Mattilsynet charges fees for handling of applications and the applicant needs to provide the correct invoice address in FOTS.

NOTE: NMBU and many other public institutions (like VI) have electronic and centralized invoicing systems requiring that correct invoice address and invoice reference is provided.

1. **Invoice reference/address for users at NBMU:**

If the fee should be paid by funds that the applicant has on NBMU, the following information should be provided:

a) Invoice reference:

Provide your resource number / employee number at NMBU

If in doubt, please contact the economy advisor at your institute/department.

b) Invoice adress:

NMBU, EHF-faktura, Org.nr. 969 159 570

2. **Invoice reference and address for external users:**
   Provide *correct invoice address and valid reference number* (contact your institution for advice).

   Most public institutions have centralized invoice adress, for example the invoice adress of the Veterinary Institute:
   Veterinærinstiuttet, EHF, Org.nr. 970 955 623

Remember also to provide valid reference number!

Confidential information

The right for the public to access official information is a fundamental right in Norway. However, it is possible (based on the Norwegian Public Administration Act and the Norwegian Freedom of Information Act) to withhold sensitive/confidential information. In is it mostly animal welfare organisations and journalists that request access to FOTS-applications.

REMINDER: The field marked in RED and with a globe in the FOTS appliation must not contain confidential information nor identify persons or institutions as these fields will constitute the EU Public summary which will be published in the European Commission ALURES database.
Do the application contain confidential information. YES/NO.
If YES, please refer to relevant act(s) and regulation(s) The relevant Acts are § 13 in the Norwegian Public Adminstration Act and/or the § 13 in the Norwegian Freedom of Information Act (contact PMSK if you need advice) Common/legally accepted reasons for withholding information include: - patent process - protection of IP rights (non-published data, competitive research areas, novel ideas) - economoical/business relations
If yes, which information do you want to keep from public access? Product sensitive details are very seldom required in an ethical application. Mattilsynet will rarely need sensitive information in their review of and decision on an ethical application. Generic information related to the type/class of test substance will usually be sufficient and equally relevant substitute for sensitive information. The **sections of the application that is to be exempt from access must be specified** – the entire application cannot be exempt. If possible, it is recommendable to only include sensitive information in attachments (and anonymize or generalize the information in the main FOTS application form) NOTE: If the application contains confidential information, Mattilsynet will not decide on the matter of confidentiality until *until they recieve a request for access from the public*. If Mattilsynet receives such a request, the applicant will normally be contacted by Mattilsynet and consulted. In order for Mattilsynet to withold information they have to doument that there are legal grounds (e.g. authorization according to relevant §§ in the Public Administration Act and the Freedom of Informaiton Act).If Mattilsynet decides that the applicant has valid legal grounds and the information is witheld, the one requesting access can still apeal Mattilsynet´s decision. Then the applicant will be consulted again. It is not uncommon that NGOs and journalists appeal/disputes decisions on confidentiality made by Mattilsynet. The appeal is handled by the head office of Mattilsynet (Hovedkontoret). The applicant

should be consulted by Mattilsynet in such cases. **Applicants responsible for applications containing sensitive/confidential information is recommended to seak legal advice in their institution in case of such disputes regarding public access.**

NOTE : If the applicant indicate that NO information is confidential, Mattilsynet will release the full FOTS application (including attachments etc) if they recieve a request for access of information from the public. Then the applicant will *not* be consulted nor notified.

Applicant and participants (co-workers)

All participants that are involved in planning or performing procedures on live animals in the experiment must be registered in FOTS and listed as participants in the application.

NOTE:

- If a person is not listed in the FOTS-application, they are NOT allowed to participate in planning or performing the experiment! **All participants needs to fullfill the legal requirments** for competence suitable for their role in the experiment.

- You can add co-workers after the FOTS-application has been approved. See the section on Changes in approved applications

Institution:

Name	Access	Course in animal research:
Applicant	NA	
Participant 1	Read or write	
Participant 2	Read or write	
Etc.	Read or write	

Add all co-workers. The applicant can decide whether the participant can only read the FOTS-application or they can be given the right to write.

If a planned co-worker is not previously registered in FOTS, the responsible applicant must send name, telephone number, mail address, course and training documentation (pdf copy of course certificates and documentation of the required practical training) to PMSK.

NOTE:

- It is the responsible applicant that has the main legal responsbility for the content of the application and also for compliance when experiments are being performed.

- Personnel that only do ex vivo work (handle animal cadavers, organs or other samples after termination) and/or personnel that only assist in data capture without handling live animals are *not* considered participants and are hence not relevant to include in an ethical application. The same goes for the permanent staff at approved animal facilities at NMBU. NOTE though, that the clinics at NMBU are not approved animal facilities (experiments undertaken in the clinics are to be regarded as field experiments).

- Information on how to add a new co-worker to *an already approved FOTS-application* can be found in the section on Changes in approved FOTS applications in this guidance document.

Background and purpose

Purpose:

Select the relevant purpose in the **drop-down menu**.

Mattilsynet has published guidance related to selection of purpose . As this informaiton is only available in Norwegian, a translation of the information from Mattilsynet is provided below:

The purpose "Basic research"

The purpose "Basic research" should be used for studies of fundamental nature, such as studies of normal and abnormal structures, phenomena, or basic laws of nature.

The sub-purpose "Other" should only be used if there are no other adequate categories.

The purpose "Translational and applied research" with various sub-purposes is to be used for applied and translational research (Section 10 b and c of the Laboratory Animal Regulation).

- Research related to animal diseases should be assigned to the purpose "Translational and applied research" and sub-purpose "Animal diseases and disorders".
- Experiments with different feed and feed ingredients for fish or mammals should be assigned to the purpose "Translational and applied research" and sub-purpose "Animal nutrition".
- Experiments with fish and mammals that are primarily concerned with welfare, e.g., testing of slaughter methods, should be assigned to "Translational and applied research" and sub-purpose "Animal welfare".
- Trials with vaccines for fish that are under development must be specified as "Translational and applied research" and sub-purpose "Animal diseases and disorders".
- Trials necessary to test batch potency for fully developed vaccines (vaccines with marketing authorization) must be reported as "Regulatory use and routine production", with either the subcategorie "Regulatory use", "Quality control (incl. batch safety and potency testing)", "Batch potency testing", "Legislation for medicinal products for veterinary use and their residues" and "Legislation satisfying Union requirements" (in cases where there is a concurrence between the regulations of Norway and the EU).

The purposes **"environmental research" "Conservation of species" or "Protection of the environment for the sake of human or animal health or welfare**" are appropriate for studies related to habitate use, loss of biodiversity, pollution, epidemiological surveys among wild animals, etc.

The experiment's objectives

Give a short presentation of the background, purpose and objectives addressing scientific unknowns, and/or scientific or clinical needs or educational needs.

Clarify the current state of knowledge on which your project intends to build. Explain the way in which the project will help to advance knowledge through filling a knowledge/information gap.

As a general rule one og more **clearly defined hypothesis** should be described. However, it is acceptable and normal that early phase projects often are descriptive and/or explorative by nature, with few or no defined hypotheses. All other projects, and particularly projects describing continuation of ongoing research project, are expected to describe one or more hypotheses that warrant the activity and provide context to the study design and practical performance.

NOTE: Keep in mind that this text field constitute a part of the public summary and therefore should not be too technical (avoid abbreviations, literature references and complicated scientific terminology) and avoid any confidential information.

For complex/larger projects, it is advisable **to attach a more through description of background and objectives**. Where relevant, **literature references** are important to include such an attachment. A list of references can also be included as attachment

NOTE: Attachments cannot replace requested information in the FOTS-form. Therefore all fields in FOTS needs to be filled out properly. Attachments should be used to supplement and provide additional informaiton that is not suitable to include in the online form.

What are the potential benefits likely to derive from this project?

'Potential benefits' are to which extent humans, animals, plants, or the environment may potentially benefit if the project meets its objectives. It relates to the value that may be placed directly on the outcomes of the programme of work, both in the short term and taking account of possible longer-term impact.

Describe scientific and societal utility, directly and indirectly: Who will benefit? In what way, and what will it mean for science and/or society? Both immediate/short-term and long-term benefits should preferably be addressed.

It can be useful to address some/or all the following points in your application to provide detailed information **about the benefits of your project**:

- Wherever possible, "increased knowledge" as the primary benefit should be linked to a more tangible strategic goal, even though any wider benefits may be much further in the future and less predictable.
- Explain why the benefits go beyond "it would be nice to know".
- Scale of improvement (for humans, animals, or the environment) and burden to society of the problem (both in basic and applied research).
- Basic research driven by hypotheses needs to confirm that the hypothesis is scientifically sound and realistic
- In some areas of basic research expanding knowledge can be a suitable objective in its own right – but *should always be linked to dissemination* of results, whether positive or negative (having regard to intellectual property), and potential longer-term benefits.

Common short-comings in applications:
Failing to adequately adress benefits (lacking wider context; unsubstantiated/unrealistic claims of potential benefits; benefits not linked to the objectives set out in the application).

When assessing a FOTS application Mattilsynet will perform a **Harm-benefit analysis,** in which the potential benefits of a research project are weighed against the harms likely to be caused to the animala. A judgement is made as to **whether the likely harms are justified by the likely benefits.** *This judgement is fundamental with regard to granting or rejection of the application, and it is the applicant that must provide enough information about benefits and harms, in order for a meaningful HB-analysis to be performed!*

Research animals (characterisation, severity, anesthesia/analgesia, etc.)

Animal species and strain/line, age, and weight

When using different strains of laboratory rodents, each strain must be **registered seperately** . **Use correct scientific names for strains/substrains/lines.** For commercially available strains of laboratory animals it is advisable to include strain/stock number and/or web-link to the specific strain, for example:

C57BL/6J, strain no. 000664, https://www.jax.org/strain/000664

Specification of age, weight and duration of the experiment need to be in accordance with each other (e.g. if it is stated that 4 weeks old male Wistar rats will be used, it cannot be stated that the start weight is 400g). Growth- and weight curves for commercial available laboratory rodents can be found at the web page of the suppliers: Charles River; Envigo; Janvier; Taconic;The Jackson Laboratory

NOTE: if you plan to use a new strain, please contact the animal facility in advance so that availability and microbiolgical health status of the animals can be checked at an early stage of the planning phase.

Number of animals:

The number of animals stated here **must conform with what is stated under "Calculation of numbers of animals".** NOTE: *If the numbers in these two sections of the application diverge, the application will automatically be returned to the applicant for revison.*

Number of reused animals (cf. § 17)/Reuse not applicable:

Reuse means using animals in a new FOTS id that have previously been used in another experiment (another FOTS id). Multiple planned procedures on the same animal in the same experiment (same FOTS id) *does not* represent "reuse".

NOTE : the regulation is strict on reuse, requiring special grounds for allowing reuse (c.f. § 17 in the Norwegian Regulation). This is to reduce the harms to individual animals.

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 and is registered in FOTS).

Duration for the most affected individual animal (d, h, min).

The duration consitute the time period from when the animal is included in the experiment until it is excluded.

It is the maximum duration of the experiment for the most affected individual animals that is to be stated. Assumptions, averages, or the time for doing the surgical intervention alone will be erroneous and misleading.

Information about the duration for the individual animal is vital for review of the application and for follow-up when the experiment is being carried out.

The duration must be based on the needs of the scientific endpoints, not what entails the greatest possible flexibility. Acclimatization, where no procedures occur, does not count as part of the duration of trials.

What are the expected severities and the numbers of animals in each severity category?

The number of animals assigned to the different severity categories must conform what is described under "procedures" and "adverse effects" in the Methods part of the application!

The severity categories are defined as follows (according to increasing severity):

I. Non-recovery: Experiments which are performed entirely under the same general anesthesia from which the animal shall not recover consciousness.

NOTE: Non-recovery experiment is often also referred to as "acute experiment" or "terminal". This category **only applies** for animals that are: anesthetized, and all the procedures are performed under anesthesia, and the animal killed *while still being in the same anesthesia*. If any regulated procedures (like for instance an injection or blood sampling) is performed prior to anesthesia, it is not a non-recovery experiment.

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

NOTE:

- experiments that result in severe pain, suffering or distress, which is likely to be long-lasting and cannot be ameliorated, is prohibited (§ 13)
- Applicants are expected to **consult the examples provided** in Part III of Appendix B in the Norwegian Regulation (equivalent to Part III in Annex VIII of the EU directive).

For further guidance and examples of severity classifications, the applicant should consult the EUCommissions Guidance Document on Severity Classification

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 **genetically altered animals (GAA)**, including animals with genetic defects that do not arise from genetic modification, are to be considered.

"Harmful or deviant phenotype" is to be understood as an animal who is likely to experience, as a consequence of the genetic alteration pain, distress, suffering or lasting harm equivalent to, or higher than that caused by the introduction of a needle in accordance with good veterinary practice (c.f. Norwegian regulation and Directive 2010/63/EU).

Provide a description of the phenotype. If the clinical effects of the altered phenotype depend on the age of the animal, describe the typical progression of the alterations and the age at which the animals will be used and/or terminated.

If you claim that a genetically altered animal line does not have a harmful phenotype *this claim needs to be documented!*

NOTE:

- "genetically altered animals" include genetically modified (GMOs: transgenic, knock-out and other forms of genetic alterations) and spontanous mutant animals
- breeding and use of GAA lines is subject to application until the applicant has completed an Animal Welfare Assessment as required by the European Commission, and documented the absence of a harmful phenotype
- Induced models, like for instance high-fat feeding to cause obesity/metabolic syndrom shoud not be described here. **Induced models should be described in the Methods section.**

Describe which precautions, efforts and/or treatments the animals will be given in order to safeguard their wellbeing and welfare and when this will be relevant:

Only relevant to fill out if you will use genetically altered animals.

Actions can range from altering of the diet (e.g. autoclaved water/feed to immunocompromised animals), altering the husbandry routines (e.g. aseptic housing and handling for immunocompromised or increased frequency of cage changes for diabetic animals due to increased urine production), to more frequent monitoring routines, 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.

Sedation, analgesia and anesthesia:

Appropriate use of anesthesia and analgesia is very important information during application review. Information on this topic is quite often incomplete in studies involving fish and laboratory animals, and the applicant is advised to contact PMSK for advice if in doubt.

Anesthesia and analgesia has to be described in terms of:
- active ingredient
- concentration (mg/ml)
- dose (mg/kg or similar)
- administration route
- adminsitration frequency
- duration of administration.

NOTE:

- The **frequency and duration of post operative analgesia** treatment is very important information which also have to conform with monitoring frequency/supervision of the animal

- Pre-emptive analgesia is a general requirement for all anaesthetic protocols. Isoflurane or other anaesthetics that lack analgetic properties are not allowed to use as single agents for surgery or other painful procedures. Pre-emptive analgesia is also required for non-recovery experiments

- Several variants of common anesthesia mixtures for rodents and rabbits are known in the literature (e.g. at least 3 different mixtures for rodents containing Zoletil are known, "Zoletil mixes"). **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 provided.**

Double-check that the anesthesia and analgesia protocol concurs with the description in the Methods section.

Use of neuromuscular blockers:

The Norwegian regulation states the following (§14): "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".

Analgesia not applicable/Rationale for why analgesia cannot be used

You should ***only*** **tick of this alternative if the procedure will cause pain, but 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 (cf Norwegian regulation § 14 and Appendix B, 3f).

What will happen to the animals kept alive at the end of the procedure?

Not relevant for studies where the animals will be euthanized at the end of the experiment.

It is reminded that "re-use" means using animal in another FOTS application. (Performing multiple procedures on animals included in the same FOTS-application *does not* represent re-use)

"Returned" can for instance be returned to owner (in case of companion animals), or to the farm, or to the wild

"Re-located" (in Norwegian: "Omplassering"): not often used, can be applicable for special field experiments where wild animals are moved to a new location/habitate.

Calculating number of animals

Explain the choice of species and the related life stages

Provide the scientific justification **and** relevance for the chosen **species, strain, genotype, sex, and age class.**

When the species is the "target" of the research (e.g. not used as a model organism), then provide information on selected age, size, sex, and breed if relevant.

Give the rationale and justifications for the numbers of animals that will be used.

The justification and **prospective calculations** on the required number of animals is a common shortcoming in applications.

The Regulation (§ 6.2) specifically requires that a **pilot study** is carried out if there are uncertainties about the number of animals needed (or if the effect on the animals of new methods are unkown).

The Regulation (§§ 9, 11) also requires that the number of animals used in experiments should be *reduced to a minimum without compromising the objectives of the project, and that the experiment should be designed in order to use as few animals as possible*.

Delayed processing of the ethical application is likely if animal numbers are not justified by valid prospective calculations. If (pilot-) studies with the same or similar animal models have been previously performed or are available in the literature, the results from these should be used for prospective calculation of required number of animals. Refer to previous FOTS ids from pilot studies and/or refer to literature of previous similar experiments when relevant.

NOTE: The number of animals must be in accordance with the numbers stated in the section «Research Animals».

NOTE: Any **replication** of the experiment and/or experimental groups needs to be justified.

In some experiments (e.g. surgical interventions, post mortem processing of organs/tissues etc.), a certain degree of technical 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, is then reasonable to include to compensate for excluded animals. However, the extra animals needs to be justified and reasonable and included in the total number of animals. Do not describe the need for 100 animals and apply for 110 (under «Reseach Animals) without explaining why 10 extra animals are needed.

Calculating the number of animals in breeding projects (i.e. FOTS application needed to breed animals with a non-documented or harmful phenotype) can obviously be difficult. The input that should be included to calculate the estimated number of animals is fertility rate, genetics and how it affects the number of offspring with the desired genotype, and the number of offspring required for experiments.

Describe all experimental groups and group sizes. A table describing the groups and group sizes may be added as an attachment to this application.

NOTE: tables copied directly into the text fields in FOTS and table-like organization of data directly in the text fields becomes chaotic nonsense in the pdf print-out that is generated when the application is submitted. **Tables are often very illustrative, but include tables as Attachments**.

For complex project with many different animal groups and/or many different procedures/interventions/tests a **timeline or flow chart should be included as attachment** in order to get an overview of «what happens when».

Describe the statistical method used to determine the number of animals. If statistics can not been applied, describe why.

It is not sufficient to write “Power analysis” or “Resource equation” and not provide any further information. If Power analysis, Resource equation or similar prospective method of calculation have been applied, the input parameters and justification for the chosen values of these parameters should be included, e.g. like size of the effect of biological parameter of interest, variation, desired power, significance level, etc. Similarily, it is not acceptable to write “Not-relevant” without further explanation. If you in other parts of the application discuss the need for “statiscical significant results”, prospective statistic should in most cases be included.

Alternatives/3Rs

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?

The requirements for documenting the evaluation of possible alternatives to animal experiments are stringent in the legislation. Stating “not relevant” or “in vivo studies are the only ones that will answer the research question” will *not* be accepted.

Assessment of replacement is relevant for all type of experiments/species. You need to describe why methods that are not harmful (according to the definition in the regulation) cannot give answer to the research question. For instance, why is it necessary to take a blood sample?; why do you need to tag the fish? Etc.

If in vitro studies have been conducted prior to or in parallell with the animal experiments this should be describe, and an explantation should be provided why the use of animals is still needed for the research in question (e.g. which questions/investigations cannot be achived using in vitro methods or other alternative methods).

To fulfill the legal requirements the alternatives must be presented *as objectively and in depth as possible with a presentation of pros and cons of available alternatives versus the applied use of research animals*. Only presenting your own views and conclusions on the relevance of alternatives will not be sufficient.

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 and the use of appropriate design.

Critical review of how and when control animals are also relevant. Performing an experiment step-by-step (in cohorts) and analysing data before including further animals/new cohorts may also be an effective way of reducing animal numbers.

If your sampling is opportunistic and/or sample size will be decied by external factors (like for instance weather conditons when performing field work; the cost for equipment like GPS-transmittors; the willingness of owners of companinon animals to contribute with blood sample of their animals; or any other restrictions related to the possibility to obtain samples) you must provide convincing scientific arguments on what is the minimum number of samples that will be necessary in order to get meaningful/valid results.

Refinement

What measures have been planned to optimise the wellbeing and welfare of the animals? (Keywords: analgesia, anaesthesia, endpoints, environmental enrichment, surgical techniques, sampling techniques etc.)

Experience from prior (pilot) experiments or literature must be used to reduce and refine future protocols with the goal to perform the planned experiment as carefully as possible with regard to animal welfare.

NOTE: if the methods that will be used are new and the effects on the animal is unknown, the regulation demand that a pilot study is carried out.

Some key words regarding refinement include:

- Proper monitoring of the animals and early stop points (humane endpoints)
- Appropriate use of analgesia
- Appropriate acclimatisation and adaptation (habituation) of the animals to handling and other procedures when relevant
- Consideration of the animal´s natural needs (use of environmental enrichment, limit social isolation of social species etc)
- Providing support therapy (heat, fluid, recovery gels, etc.) following surgery

Please provide reasons for the planned fate of the animals after the procedure

In most studies involving laboratory animals, the animals will be euthanized as samples/tissues are needed for further ex vivo analysis.

Methods section

When writing ethical applications and performing animal experiments, one simple rule applies:

Write what you do - and do what you write!

The description in the application must enable Mattilsynet to assess: the planned technical design and methods used in the experiment, how this will affect the animals and the research results, and how the study will meet the described study objectives. Describe all the planned procedure **in a chronological order** so it is possible to evaluate the cumulative effect on the animals and to understand “what happens when”. The technical methods should also be described clear in order to facilitate evaluation of compliance when the experiment is actually being carried out.

NOTE:

- Do not include excessive information on ex vivo analyses that will be performed after the animal is terminated. A summary/brief descripton is sufficient to demonstrate which data that willl be generated from the animal experiment

- Refer to attachments (literature, figures, tables, flow-charts) *when relevant* to supplement the text, but attachment should not be a substitute for submitting a complete text in the methods section of the online application form.

Preparation of the animals before the experiment
Describe any purchase, transport, quarantine/acclimation, housing, environmental enrichment, feeding regime.

Answer all the points listed. Under housing include cage/tank type and size, number of animals in cage/bin/tank, type of environmental enrichment, feed/water regime etc.

For mammals in animal facilities: if the animals will be handled frequently during the experiment, a period of gradual adaptation to handling should be included. Similarly, use of equipment that requires an activity that is not voluntary and/or normal (e.g. running on a treadmill) will require gradual training and adaptation of the animals prior to study start.

NOTE:

- If the housing conditions will be different from recognized husbandry practices, describe it clearly. This includes single housing of social species (like rodents and pigs). If single housing is considered necessary, justification as well as indication of necessary time should be provided in the. Similarly, other deviation from standard housing conditions (light, temperature, altered feeding regime etc.) needs to be thoroughly described

- For rodents: 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.

Which procedures will be applied to each animal during the experiment *(e.g. restraint, handling, tagging, internal 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 location, method administering, and volume to be administered have to be described. Describe incarceration/immobilisation necessary to perform the procedure.*

- All procedures, also those *not* involving surgery or invasive techniques, must be described.

NOTE: attachments may supplement and expand the information supplied in this section, but should not be a substitute for submitting a complementary text in application form.

- ID marking must be described, and also geno-/phenotyping if relevant. If ID-identification of the animal is regarded unnecessary, this should be stated (in order for it not to appear as an omission)

- Write the text chronologically so that it is clear when the different interventions and procedures are taking place on the individual animal. Take into consideration that following many procedures, animals need a recovry period before the next procedure

- If multiple interventions are performed and/or it varies between different groups of animals, attach and refer to a timeline or flow-chart to supplement what is written in the text so it is possible to evaluate “what happens when” with each individual animal. The number of times and when an intervention/procedure is being performed on the animal must be clearly stated (in order to evaluate cumulative harm/welfare effects). The expected overall (cumulative) effects on the animals of all planned procedures have to taken into account and described.

NOTE: if multiple interventions are performed you need to consider the need for recovery periods in between different interventions (e.g. anaestheisa may cause intermediate weightloss; blood can not be sampled in too large volumes too frequently; etc).

- The regulation has a general requirement for anesthesia when performing procedures on research animals. However, anesthesia can be omitted *if anesthesia is considered more stressful than the procedure itself* or if anesthesia is considered incompatible with the study purpose. Literature clearly document that physical restraint is very stressful for rodents. Only routine procedures, that can be completed rapidly by skilled technique and require short periods of physical restraint, should be performed under physical restraint only. Routine SC/IP injection and standard blood sampling are examples of such procedures. When physical restraint or anesthesia will be used for sampling, injection and/or other procedures, the number and duration of (repeated) procedures, anesthesia and physical restraints must be described.

Anesthesia and analgesia are central elements in the cost-benefit analysis and one of the topics that most often give rise to questions and requests for change.

Even if anesthesia/analgesia has been described in the table in the "Animal section" of the application, it is recommended to include a complementary description of the timing of the anesthesia and analgesia protocols in the methods section as well. Analgesia, observation time after conclusion of the surgical intervention and supportive therapy (heat, fluids, other) should also be described. Ensure that the drugs, dose levels and frequency of anesthesia and analgesia in the Methods section and Animal sections are identical.

- Provide a detailed and technical description of all interventions:
    - If surery is performed: include preparation, the surgical interventions, equipment used; wound closing, post operative monitoring, etc.
    - Administration of substances (oral, injections, etc): provide VOLUME, DOSE, ADMINSTRATION METHOD AND FREQUENCY
    - For guidance on the max. recommended volumes for injection/oral administration to common laboratory animals see e.g.. this article: http://onlinelibrary.wiley.com/doi/10.1002/jat.727/epdf
    - Add all test substances, drugs and chemicals that the animals will be exposed to. Dose levels are always relevant, but remember to also include information on dosing VOLUME.

NOTE: If the test substances might cause adverse or toxic effect (intended or unintended) the expected clinical effects of the animals have to be clearly described. If you state that the substances will *not* have any effects on the animal, references needs to be provided – the burden of proof is on the applicant! A pilot study will have to be performed if the effect on the animal is unknown (c.f. Norwegigan regulation §6).

- The VOLUME to be administrated is very often lacking. This is essential information in order to evaluate if the volumes are adapted to the animal species and animal size/age. Please use and refer to published guidelines regarding max. volumes (for rodents see e.g. http://onlinelibrary.wiley.com/doi/10.1002/jat.727/epdf)

Also, provide details on dose level (volume and quantity of active substance) per dosing, number of dosages, administration method and speed of injection for iv. (ml/min or ml/kg/h).

- BLOOD SAMPLING: Include volume per sample, number of samples, sample frequency and sampling technique. This is essential information in order to evaluate whether the planned blood sampling regime is adapted to the animal species and animal size/weight/physiological status. Follow published guidelines. UKs 3R-center

(NC3R) has a very useful webpage providing guidance for blood sampling of common laboratory animals.

NOTE:

- terminal blood sampling from the heart from rodents requires surgical anaesthesia (use of CO_2 is not allowed)
- the retro-orbital blood sampling technique for rodents is not a method that is recommended and will usually not be allowed in Norway as routine method

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).*

Describe clearly the different groups; the scientific endpoints/outcome measures, and how animals are allocated to groups (randomization or other procedure); describe which analyses that are performed and if blinding is being used. For larger/complex project it is advisable to attach more information in tables/flowchart

NOTE:

- do not repeat or reiterate text from other sections in the application
- use tables or figures as attachment to illustrate more complex/large projects
- make sure that you use the same name/reference to the atttachment in the text as the file name

What are the expected impact/adverse effects on the animals. *Examples: pain, weight loss, inactivity/reduced mobility, stress, abnormal behaviour, and the duration of those effects?*

(in the pdf that is generated of the application, the title of this field is “Reason for indicated accumulated severity for the animals that are most affected”)

The assessment of adverse effects must conform with what is listed under “Procedures” and to the section where animals are allocated to different severity categories!

You must address the potential adverse effects (= harms) and your description and assessment should *be systematic, realistic, and based on scientific and clinical knowledge*. If there are uncertainty which harms that will be caused, the legislation require that a pilot study is performed.

NOTE: Assessment of potential adverse effects includes *more* than just evaluating potential pain, it also includes stress, aversion, any limitations in expressing natural behavior (including modifications on the housing, husbandry, and care standards), etc.

Describe which harms that may occur, when they might occur, and for how long (duration). If different animal groups will experience different harms, be clear and systematic when describing the various groups. If multiple procedures are performed, consideration must be given to the cumulative strain/burdens (and the need for recovery periods in between to reduce such burdens).

If you state that “no adverse effect” is expected, it needs to be validated/documented – the proof of the burden lies on the applicant!

NOTE:

- The defined humane endpoints will significantly influence the level of severity, e.g. the earlier you can terminate/stop, the lower the strain will be on the animal. Remember that

humane endpoints are more than euthanasia, and alwasy take the humane endpoints into consideration when you are assessing the overall harms on the animals.

- Timing and frequency of interventions will inflict on the level of harm and severity
- Allocating sufficient and appropriate recovery periods may contribute to reduce cumulative effect and consequently also reduce level of harm

Follow-up and supervision *before, during and after procedures.*

Take into account all the adverse effects that can be expected during the whole experiment = "**critical periods**". This provides the foundation for the requirements for follow-up: **what to look for and when**. Proper identification of critical periods is also important for definition of appropriate humane endpoints.

You must describe monitoring points and monitoring frequency.

Animals should be health assessed at inclusion (to assess whether they are "fit-for-experiment"), as well as during and after procedures.

All animals must minimally be observed once daily, but for some experiments more frequent observation of the animal than 1/day is needed either during special critical periods of the experiment or throught the whole experiment.

For non-recovery experiments and for experiments involving surgery: assessing the health status of the animal *prior to* anesthesia as well as continuous monitoring of anesthetic depth and the animal´s physiological condition during the surgical procedure are critical components of follow-up and supervision and must be included.

If no adverse effect are expected (again: the burden of proof is on you the applicant!), it will be sufficient to state that the animal will be under "standard daily observation by the animal care taker staff at the facility". In all other circumstances a detailed plan for follow-up and supervision of the animals have to be provided with identification of critical periods, welfare assessment scheme and frequency of observation.

USE OF SCORE SHEETS
A score sheet should be used when relevant.

- Score sheets should be used where significantly reduced general condition/animal welfare is expected, to quantify and document the overall burden and measures in relation to pre-defined human endpoints. Score sheets are especially important to use where one is uncertain of, or does not expect exact and clear human endpoints. Then the total burden on the animal becomes particularly important to document using the score form
- Score sheets should not be automatically used in all types of experiments. In experiments where it is uncomplicated to define clear and unambiguous human endpoints, these endpoints can be clearly described in the FOTS application, and one does not need to use a score form. Score sheets shall not be used in terminal or mild experiments where significantly reduced general condition is not expected.

The score sheet should be species- and procedure specific with relevant, measurable clinicial parameters. It should include examples for the different scores and which measures that will be implemented following a specific sum of score. **An example Score sheet for rodents is attached at the end of this guidance document.**

NOTE: When score sheets is indicated/required:

- You must adapt the score sheet with relevant parameters and assessment criteria suitable for your particular experiment. For example, if surgery is peformed assessment of post-operative pain and wound healing is essential. If weight loss is expected, weighing the animal as well as body condition assessment must be included.
- You must refer to its use in this section of the application form (e.g. under "Follow-up and supervision) and clearly indicated on which animals, which time periods during the experiment, and which monitoring frequencies that will be applied
- Make sure that the score sheet is attached to the FOTS-application
- Score sheets MUST be used on relevant animals during the experiment in the periods/frequency described in the FOTS-application. Failure to use a score form during critical periods of a project represents a deviation
- When conducting the experiment, the score sheet should be available in the animal housing room so that the staff of the animal facility can assess the assess the applicant's observations in relation to the animals' current situation
- Score-sheets needs to be archived for 5 years and available for inspection by Mattilsynet

Method of euthanasia *If animals are to be euthanised:Which method of euthanasia will be used (cf. regulations § 16, part 2 and appendix C)?*

Appendix C in the Norwegian Regulation (equal to Annex IV in the EU directive) contains **a table listing allowed euthanasia methods** for various species that you need to consult.

NOTE:

- for several of the euthanasia methods listed in App. C **there are restrictions and conditions for its use**.
- When using anesthetic overdose: Provide active ingredient , dose and administration method.

Deviating method of euthanasia *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).

This field should be left open, unless you are using a method that is NOT listed as approved method in the regulation!

Any method of killing that deviates from those described in App.C must be explicitly described and *scientific arguments provided* for why the methods in App. C cannot be used.

It has to be scientfically documented either 1) the method is as equally effective on welfare grounds as listed methods or 2) that the listed methods cannot be used due to conflict with the research objective.

You need strong arguments to receive approval for using a non-listed method!

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.*

The purpose of humane endpoints is to prevent uncessary animal suffering, e.g. avoid harms that are not necessary to achive the objective of the study.

The described **humane endpoints in the FOTS application are binding** and not subject of discussion when the experiment is ongoing!

Humane endpoints (HEPs), are predefined criteria that determine when the procedure/experiment should be ended for the individual animal. The humane endpoints provided will heavily influence the severity category assigned to the experiment.

Subjective and little specific HEPs, which give no guidance on interpretation and actions, are often seen in applications. "The animals will be killed if they suffer unnecessarily" is an examples of a meaningless HEP that is not accepted.

HEPs should be precise and specific and based on measurable changes in the animal (biochemical, behavioural, clinical).

HEPs should be set as early as possible in relation to the scientific objectives of the experiment. In many (most) experiments involving laboratory animals, it is unnecessary that the animal become critically ill/moribund as the objective often is to investigate earlier stages of the disease development rather than severe or advanced stages.

NOTE: §11 in the Regulation states the following: Death as an endpoint should be avoided as far as possible. If death is unavoidable as endpoint the experiment should be designed so that:

a) as few as possible animals dies
b) the duration and intensity of the suffering is reduced as much as possible, and
c) a painless death is ensured as far as possible

In this contexts **"death as endpoint" means that animals are allowed to deterioate to a point where they are moribund/dying without interventions.** Usually there is no need in most experiment to push it to this extreme end. Usually the animals can be euthanised before they become terminal ill.

As a general rule the max. allowed weight loss in laboratory animals should not exceed 10 % unless there is scientific reasons for allowing a higher weight loss. In some animal models a transient higher weight loss is expected. In such cases this must be clearly described (incl. when weight loss occur, expected % of loss, and when regain of weight is expected)

The HEPs should be adjusted to the specific experiment, e.g. with clear, relevant clinically measurable parameters.

When **Score sheets are indicated/required, you must refer to it in the text field here**. See also information above under "Follow-up and supervision of the animals" as the Attachment 1 score-sheet

Humane endpoints are **also relevant for non-recovery experiments** (inability to maintain the animal in stable surgical anesthesia or critical, unintended change in physiology for example due to bleeding) **as well as for breeding projects** (deviations from defined/approved phenotype, max. number of litter pr animal etc)

Which actions will be taken if animals reach the humane endpoint *(examples: treatment of symptoms, reduced exposure, or euthanasia)*

Therapy by analgesia, support-diet (for instance recovery-gel for rodents or i.v. fluid for larger laboratory animals), antibiotics or euthanasia are 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 actions (other and earlier measures than euthanasia). Such measures can be, for example, temporary halt in procedures to allow for recovery, nutritional gel, soaked feed in the bottom of the cage, fluid treatment, etc.

Attachments to the FOTS application

NOTE: Attachement should be supplement to the online application form when needed. **Attachment should not be a substitute for submitting a complete text in the online application form.**

All text field in the online form should be completely filled out, and a statements like “See attachment for details” and no further text in the text field of the FOTS form will be returned to the applicant for revision.

Examples of attachments:

A. Confirmation from animal faciltiy when performing the experiment at one of NMBUs approved animal facilities. Not relevant for field experiments
B. Score sheet when relevant
C. Detailed project description for more complex/larger experiments
D. Table with experimental groups and treatments
E. Timeline or flow chart illustrating the various phases, interventions and duration of the experiment
F. Relevant scientific publications as reference list or as pdf (latter should only be included if essential for the evaluation of the application)

NOTE: Too many and perifer attachment will increase the handling time of the application. Attachments may be very useful, but only add attachment that are central for evaulation of the application.

Changes in approved FOTS applications

It is not allowed to deviate from the approved FOTS-application without applying or notifying the Food Safety Authority (Mattilsynet)!

You can only apply/notify changes (including extension of approval period) for FOTS-applications that have a valid approval.

Depending on the nature of the change you will either have to “**Apply for change**”; or you will have to send a “**Notification of change**” (see the table below for examples); or if the changes are too substantial/deviating too much from the original FOTS-application – you will have to submit a completly new FOTS-application.

The functions for applying/notifying changes in a particular FOTS-application, can be found in the left hand side menu under the specific FOTS ID.

When an application/notification of change is submitted in FOTS, it first goes to PMSK for control. The PMSK will consider whether the change fall under the cateory of application/notification and whether it contains sufficient information.

For both application and notification of changes, the applicant must describe the following:
1) Purpose of the change, 2) description of the required changes, and 3) update project summary if relevant, and 4) For notification of changes the applicant also need to explain why the changes are considered not to have negative impact on animal welfare.

Notificaiton of change as well as extension of project approval period is free of charge. Application of changes (except for extension of approval period) are charged with a fee.

Changes that are considered to have no negative impact on animal welfare can be notified by sending "NOTIFICATION of change" (see table ahead for examples).

PROLONGATION of the approval period for the experiment always require APPLICATION for change (as it is only Mattilsynet that has authority to grant project approval).

NOTE:

- only applications that still have a valid approval can be prolonged, meaning that you must apply in due time in advance before the approval date expire if a prolongation is needed. If the approval date has expired or if the maximum approval period has expired (e.g. 4 year for experiments conducted in an approved animal facility or 2 years for field experiments), **you will have to send in a new complete FOTS application.**

- It **is possible to copy a prior FOTS-application** if the experiment will continue after the approval has expired. See chapter below.

    - It is not allowed to continue the experiment if approval has expired before a new approval has been granted by Mattilsynet!

Guidance on typical changes in approved FOTS protocols

Change	**Category**	**Comment/Conditions**
Extension of project end date (aproval period)	Application	Extending the project end date has no negative effect on animal welfare and could be notified. However, changing the end date of an approved project requires an authority that only Mattilsynet has. **Only applications that still have a valid approval can be extended.**
Expand 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**.
Altered composition of animal lines and genotypes within same species. No change in total animal numbers within species in question	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	Requires that the qualitative effects of the altered anesthesia/analgesia remains as previously described.
Including new participant	Notification	Requires that the participant can document the required competence and education. See also point below

Make a copy of a previous FOTS-application

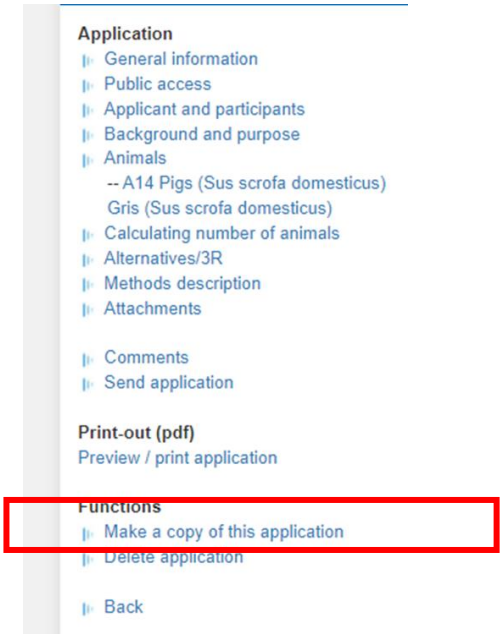
If the approval period has expired, you will need to send in a new complete FOTS-application in order to continue the experiment.

NOTE:

- It is not allowed to continue the experiment if approval has expired before a new approval has been granted by Mattilsynet!

When preparing a new application that is a continuation of a previous experiment, you can copy the former application by doing the following:

A. Log on to FOTS and find the topical FOTS id you would like to copy
B. In the left menu, under “Functions”, click “Make a copy of this application” as indicated in this figure:



NOTE:

If the previous application was submitted prior to July 2022, it is <u>not</u> recommended to copy the application. This is due to that FOTS was substantially changed in July 2022 with many new text fields (in particular those marked with a globe). Consequently much information in the old application will not be transferred at all or not correctly to the copied version.

ATTACHMENTS

ATTACHMENT 1 CONFIRMATION ANIMAL FACILITY

FOTS ID:	Click or tap here to enter text.
Responsible applicant:	Click or tap here to enter text.
NMBU Animal facility:	Click or tap here to enter text.
Subunit at animal facility, if relevant:	Click or tap here to enter text.
☐ I hereby confirm that I have discussed and agreed with the animal facility that the facility has the capacity (including necessary personell and infrastructure) for the planned experiment as described in the FOTS application ☐ I am aware that animals cannot be bred, purchased, or in anyway prepared for the experiment before Mattilsynet has approved the FOTS application ☐ I am aware that this form does not release the applicant from responsibility to maintain close dialogue with the animal facility in the further planning and execution of the experiment	
Date:	
Signature of responsible applicant:	

ATTACHMENT 2 EXAMPLE SCORE SHEET

EXAMPLE SCORE SHEET for assessment of health, welfare and humane endpoints adapted to rodents

NOTE:

- the score sheet needs to be adapted to the specific experiment with relevant observation parameters
- Monitoring frequency and measures must be clearly described in the FOTS-application (in the Methods section, point “Supervision and follow-up..” and “Humane endpoints”.
- When using score sheet, always clearly refer to this in the FOTS-application form, and make sure that the score sheet is attached to the application
- When conducting the experiment, the score sheet should be available in the animal housing room so that the staff of the animal facility can assess the assess the applicant's observations in relation to the animals' current situation
- Score-sheets needs to be archived for 5 years and available for inspection by Mattilsynet

See example score sheet next page.

NOTE: the example on the next page is a general and indicative TEMPLATE (with example parameters and non-linear scale). The form must be adapted to each specific experiment with relevant expected clinical parameters and score values must be adapted to the experiment in question.

TEMPLATE SCORE SHEET RODENTS NMBU									
Score sheet FOTS ID: Animal ID: Form no:		0-3: Normal 4-6: Carefully monitor the health condition 7-9: Carefully monitor the health condition and consider euthanasia 10-12: Euthanasia							
Parameter	**Condition**	**Assessment scale**	**Date**	**Date**	**Date**	**Date**	**Date**	**Date**	**Date**
Apperance	Normal	0							
	Reduced grooming	1							
	Slight or partial piloerection	2							
	Significant piloerection, hunch back	10							
Activity level	Normal	0							
	Slightly reduced activity	2							
	Significant reduced activity	5							
	Inactive	10							
Body weight	Normal	0							
	Loss < 10%	1							
	Loss 11-15 %	2							
	Loss 16-20 %	5							
	Loss >20	10							
Grimace scale (pain)*	None	0							
	Moderate	5							
	Significant	10							
Clinical signs	*Experiment specific								
SUM SCORE									

*Grimace scales | NC3Rs

* Must be specific and adapted to individual experiments with relevant parameters

If surgery: scoring of surgical wound healing must be included.

Tumor models: size and appearance of the tumour must be included, and max. size must conform to the max. size described under “Humane endpoints” in the FOTS-application form.

See also the point “Follow-up and supervision of animals” in the Methods section for more information on the use of score sheets