

Guide to **Clinical Field Trial Licence Applications under National Veterinary Legislation**



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1 SCOPE

This guidance is intended to assist applicants in completing and submitting an 'Application for a Clinical Field Trial Licence under National Veterinary Legislation', which must be submitted as part of the licence application process. The legislation governing this process is Regulation 2019/6 and S.I. No. 36 of 2022 (hereafter referred to as the Regulations).

2 INTRODUCTION

In accordance with Article 9 of Regulation 2019/6 and Article 3(1) of S.I. No. 36 of 2022, clinical trials on a veterinary medicine for the purpose of generating data to support a marketing authorisation, or for other purposes shall not be conducted without prior licence from the Health Products Regulatory Authority (HPRA). A clinical field trial licence application form must be submitted and approved in order for work to commence on any clinical field trial. The HPRA is obliged to consult with the Department of Agriculture, Food and the Marine (DAFM) prior to granting a licence for a clinical field trial.

The Regulation defines a clinical trial as a study which aims to examine under field conditions the safety or efficacy of a veterinary medicinal product under normal conditions of animal husbandry or as part of normal veterinary practice for the purpose of obtaining a marketing authorisation or a change thereof.

In practical terms, a clinical trial aims:

- to demonstrate or substantiate the effect of the veterinary medicinal product after administration of the recommended dosage,
- to specify its indications and contra-indications according to species, age, breed and sex, and
- to specify its directions for use, any adverse reactions which it may have, and its safety and tolerance under normal conditions of use.

Regulation 2019/6 requires that clinical trials shall be carried out taking into account the international guidelines on Good Clinical Practice of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). In practice this means that clinical trials are usually conducted using test and control animals (controlled clinical trials). The effect obtained should be compared with a placebo or with absence of treatment and/or with the effect of an authorised medicinal product known to be of therapeutic value. All the results obtained, whether positive or negative, shall be reported. The methods used to make the diagnosis shall be specified. The results shall be set out by making use of quantitative or conventional clinical criteria. Adequate statistical methods shall be used and justified.

In the context of this application procedure, it is considered that a veterinary medicinal product includes pharmaceuticals, biologicals, immunologicals, and any other agents (including tissues or devices) that:

- is presented in a medicinal form
- is intended for the treatment or prevention of a disease, or
- which otherwise influences physiological functions by exerting a pharmacological, immunological or metabolic action in animals.

As the national legislation allows that certain safety and efficacy tests on a veterinary medicinal product could be considered to fall within the scope of this procedure (e.g. bioequivalence tests, residue tests, tolerance tests, etc., that are conducted using the finished product formulation), this procedure may also be used for such trials, in addition to clinical field trials. However, exploratory, proof of concept and other developmental studies are regarded as pre-clinical studies that fall under the scope of Directive 2010/63/EC and are therefore outside the scope of this application procedure.

The HPRA licensing process involves:

- the decision to grant permission for the conduct of the proposed trial,
- the designation of appropriate withdrawal period(s), in the case of trials conducted in a food-producing species,
- the establishment of any appropriate conditions for the conduct of the trial, and
- in the case of veterinary medicines that do not have a marketing authorisation, determining the quantities of test or control veterinary medicines that may be imported, supplied, used or administered to test animals in relation to the proposed trial.

3 APPLICATIONS FOR A CLINICAL FIELD TRIAL LICENCE

The application should be completed by the applicant, i.e. the person responsible for the conduct or supervision of the trial or the conduct of the associated procedures. This is the person to whom the licence, when granted, will be addressed.

The HPRA is required to complete the assessment of applications within 60 working days. However, timeframes will be suspended if applications are incomplete or incorrect and will restart only on provision of completed information. Queries raised during the assessment, or a delay in submitting responses to queries by applicants, may also cause timeframes to be extended.

The HPRA is obliged to consult with the DAFM prior to reaching a decision on an application for a trial. The HPRA requests that the applicant copies their e-submission to the DAFM at the time the application is being submitted to the HPRA. The HPRA understands that the Department assessment process will take two weeks.

It is recommended that the applicant provides a cover letter or email with the application to the HPRA, together with a brief summary of the trial. This information allows the HPRA to gauge the complexity of the evaluation task and allocate appropriate resources accordingly.

4 SECTION A – PROPOSED LICENCE HOLDER (I.E. APPLICANT) AND DETAILS OF THE TRIAL PERSONNEL AND LOCATIONS

4.1 Proposed licence holder and other relevant persons

Provide details of the proposed licence holder (i.e. the name, address and contact details of the applicant with whom the HPRA can correspond). In a commercial setting, the applicant may be the company with overall responsibility for the conduct of the trial. In an academic or practice setting, the applicant will usually be the principal investigator or veterinarian responsible for the conduct of the trial.

If the trial is being undertaken by an investigator at the request of a sponsor, the name, address of the sponsor should be provided, together with the name, address and contact details of the trial director with overall responsibility for the conduct of the trial in Ireland.

A brief *curriculum vitae* of the trial director responsible for the conduct of the trial should be provided. The purpose of this information is to ensure that the person concerned has the appropriate qualifications, knowledge and expertise to oversee the conduct of the trial and ensure compliance with any conditions attaching to the HPRA licence. The information is expected to assist the HPRA in judging the feasibility of the proposed trial.

If veterinarians, other than those already listed as the trial director, are to be engaged to perform follow up actions in relation to any adverse reactions that might occur as a result of treatment with the test product or in relation to the supervision of animal welfare during the conduct of a trial, their names, addresses and contact details should be provided. This information aids the HPRA in following up on any pharmacovigilance matters relating to the conduct of the trial.

4.2 Location details

If known, provide information on the location(s) where the trial is to be conducted. Where various qualifying practices or individual farms are to be used and their location is unknown at the time of application, the expected number of practices and farms and their geographical location should be stated (e.g. 10 companion animal veterinary practices in Leinster, or 50 dairy farms with >200 cows in County Cork).

5 SECTION B – INFORMATION ABOUT THE CLINICAL FIELD TRIAL

5.1 Trial title

The title of the clinical field trial should be summarised in less than 200 characters. Where the trial is being conducted to satisfy regulatory requirements, the word 'regulatory' should be

included as the first word in the trial title. In all other cases the word 'research' should be included as the first word in the title. Following this, the title should capture the trial objective. It is also required to include the species of test animals in the title. High-level and easily understood terms should be used, e.g. 'clinical trial to demonstrate the efficacy and tolerance', etc.

5.2 Trial information

A person shall not import or administer a veterinary medicine or test drug to an animal for the purpose of a clinical trial save in accordance with a Clinical Trial licence granted by the HPRA following consultation with the DAFM.

Information about the reasons for the conduct of the proposed clinical field trial should be provided as outlined below.

5.2.1 Regulatory requirements

If the trial is being performed on a veterinary medicine solely to satisfy specified regulatory requirements for the testing of a veterinary medicine in support of an application for a marketing authorisation:

- using established methods in conformity with the Regulation, or
- according to European guidelines relating to the testing of a veterinary medicine, or
- in fulfilment of a requirement of another competent regulatory authority for the authorisation of a veterinary medicine from the European Economic Area,

then this box should be checked.

5.2.2 Trial protocol, trial design and information on test products

In accordance with Chapter II of Annex II of Regulation 2019/6, all clinical trials on a veterinary medicine shall be conducted in compliance with a fully considered and detailed trial protocol. The Regulation requires that unless the trial is conducted with a blind design, the labelling of formulations intended for use should bear the words 'for veterinary field trial use only'. Where the labelling of the products being used does not carry such wording (i.e. the product has a marketing authorisation already), the Summary of Product Characteristics of the test product(s), together with the number of the marketing authorisation should be provided. This allows the HPRA to evaluate whether the proposed conditions of use of the product for the trial reflect those of the marketing authorisation, and to decide whether any additional precautions or a longer withdrawal period might be needed to protect animal or public health. In any case where a veterinary medicine that is not currently authorised by the HPRA or the European Commission is to be used in a clinical field trial, the quantity of product needed for the conduct of the trial must be stated (e.g. '5 boxes of 20 x 100 mg tablets of product z,' or '2 x 100 ml vials of product y'). The reason for this is to ensure that sufficient product is available for the trial conduct, while preventing unauthorised use outside the scope of the proposed trial. The quantity of test product(s) foreseen to be used will be included in the HPRA licence and may be audited by the DAFM or the HPRA.

The trial protocol or information on the trial design should be provided. The reason for this is to enable the HPRA to conduct a benefit/harm analysis of the proposed trial, and ensure the trial is feasible, fit-for-purpose and is limited to a defined sub-population of the target animals. Therefore, brief information on the trial objectives and expected benefits, as well as the procedures involved in the conduct of the trial should be provided.

In accordance with Recital 28 of Regulation 2019/6, the welfare of the trial animals shall be subject to veterinary supervision and shall be taken fully into consideration during the elaboration of the trial protocol and throughout the conduct of the trial. Whether or not the trial is a regulatory study, the HPRA considers that the 3R principles (replacement, refinement and reduction) will help underpin the design and conduct of the trial. Therefore, brief information on how each of these principles has been considered should be given, as outlined below.

5.2.3 Replacement

Information should be provided about the current state of scientific knowledge, i.e. whether the trial relates to new research in an existing and well-defined research area, or is intended to validate a similar trial conducted outside of Ireland, or for some other specified purpose. Outline why animals are required for this clinical field trial, the non-animal alternatives that were considered and the reasons why any available non-animal alternatives could not be used.

5.2.4 Reduction

The total number of animals to be used for each target species must be provided and a suitable justification for the number chosen must be given. Where possible, the number chosen as well as the trial design should be reviewed by a biostatistician.

5.2.5 Refinement

Information should be provided to show that the trial is designed so as to enable any procedures to be carried out in the most humane and environmentally sensitive manner possible. The degree of detail required depends on the type of trial envisaged. For all cases, explain the general measures to be taken to minimise harm to the animals (e.g. through the use of analgesics, rescue protocols, etc.).

5.2.6 Ethics committee approval

Indicate if the trial has been approved by an ethics committee. If so, provide copies of the following documentation:

- the trial application and protocol as approved by the ethics committee.
- the letter of approval of the ethics committee that identifies any conditions for the conduct of the proposed trial.
- report outlining any queries on the design or conduct of the trial that have been raised and addressed as part of the ethical review process. Alternatively, correspondence by hard copy or email to and from the ethics committee relating to the trial in which queries have been raised and addressed should be submitted.
- signed letter of approval from a biostatistician, where possible.

Note that it is not mandatory that clinical field trials have been approved by an ethics committee. However, such information is of value to the HPRA in evaluating the proposed trial and will minimise the time needed for the HPRA to evaluate the application.

5.2.7 Expected duration of project work

Indicate the period in months. Normally, clinical field trials shall be completed within a period of months. Where the duration of the trial lasts for more than one year, a detailed justification must be provided.

5.2.8 Expected start date of clinical field trial

Clinical field trials cannot be conducted prior to approval being granted by the HPRA. Clinical field trials are expected to commence within weeks from the date of HPRA licensing.

5.2.9 Resource details

Feasibility and resource information is a requirement for all clinical field trials on veterinary medicines. This will provide information:

- on the technical challenges or degree of complexity of particular procedures envisaged in the conduct of the proposed trial; and
- to support the contention that, if approved, there are sufficient resources available to allow the clinical field trial to be completed expertly and in conformity with the terms and conditions of any licence granted.

Clinical trials on target species which are conducted by experienced personnel who have a track record in such work, and/or where the trial is supported by a research grant or sponsorship funding are more likely to be successful than those where such supports are not available. Brief details of the available resources should be provided (< 200 characters).

6 SECTION C – PURPOSE OF THE CLINICAL FIELD TRIAL

This section will assist the HPRA in the trial evaluation.

6.1 Trial purpose

The purpose of the trial, including the expected benefits, should be outlined in <500 characters. In the case of trials that are to be undertaken to satisfy regulatory requirements, the specific type of the trial should be stated (e.g. tolerance test in pregnant animals, etc.). The information should be provided in a concise manner as this is helpful to the HPRA in preparing its assessment report of the application.

6.2 Trial details

6.2.1 Details of the test product(s)

Where a veterinary medicine is to be used that does not have a marketing authorisation in force in Ireland currently (i.e. the test drug is not already authorised by the HPRA or the European Commission), provide the following additional information in respect of each product:

- details of the product composition (e.g. certificate of product specification), and name of manufacturer.
- where relevant (i.e. in the case the product is to be administered to a food-producing animal species), a statement as to whether the active substances in the test product(s) have an established maximum residue limit (MRL), and the proposed withdrawal period(s).
- statement as to whether the product(s) contains a genetically modified organism (GMO).
- statement as to whether the product(s) is compliant with the EU guidance on transmissible spongiform encephalopathies (TSE).
- statement as to whether the product(s) is free from extraneous agents.

If a test product (other than an already authorised veterinary medicine) contains a GMO, the applicant is required to provide a letter of approval from the Irish Environmental Protection Agency (EPA), to confirm that the product is acceptable and setting out any conditions attaching to their authorisation/licence. The HPRA is not in a position to complete the assessment of an application for a clinical trial that refers to a GMO until the EPA has authorised the safety of the GMO product for use in this country.

In the case that the test product is a vaccine or biological agent that does not have an existing marketing authorisation for a veterinary medicinal product from an EU regulatory authority, the DAFM requires information on the safety of production of the vaccine concerned. This information should detail:

- the country where the product is being manufactured.
- other vaccines or biological agents being produced at the same factory.
- the steps taken to prevent cross-contamination of the product with other antigens.
- the tests performed on the finished product to check for freedom from extraneous agents.

The reason for this is to ensure that no test product is imported into this country which contains a pathogen or biological agent that might lead to the spread of disease.

6.2.2 Proposed dosage and route of administration to be used

Information on the dose and dose regimen (including duration of therapy) as well as the route of administration of the test products (including placebo if relevant) should be given. Information on any specialised equipment needed for drug delivery should be specified. Any limitations on the administration should be stated (e.g. not more than 5 ml volume at each injection site), or any special precautions to be observed during the conduct of the trial should be outlined.

6.2.3 The GLP/GCP status of the proposed trial

As per national legislation relating to the conduct of clinical field trials, the application procedure must also encompass safety tests on veterinary medicinal products in addition to

efficacy tests. In the case of safety or bioequivalence trials, in accordance with Regulation 2023/183, pharmacological, toxicological, residue and safety tests must be carried out in conformity with the provisions relating to Good Laboratory Practice (GLP) in an establishment that has a facility licence for GLP. Trials relating to the demonstration of efficacy must be carried out in conformity with the provisions relating to Good Clinical Practice (GCP). GCP is an international ethical and scientific quality standard for the designing, conducting, monitoring, recording, auditing, analysing and reporting of clinical trials on veterinary medicines, which should be followed when developing clinical trial data that are intended to be submitted to regulatory authorities. Depending on the nature of the trial, information on whether the trial is to be conducted under the conditions of GLP or GCP should be given. If the trial is not being conducted in accordance with GLP or GCP, confirmation that pre-established systematic written procedures are in place for the organisation, conduct, data collection, documentation and verification of clinical trials is required.

6.2.4 Proposed observations or measurements to be carried out

Provide information on the evaluations to be conducted on the trial animals. This should include information on relevant trial endpoints, as well as any objective tests of activity (laboratory analyses, physiological tests, etc.) required to evaluate the application. Information on whether the observations were carried out in a blinded manner should be given, as well as the frequency of the observations or measurements carried out.

6.2.5 Information on housing, husbandry and care

Provide information on the general care, housing and husbandry as well as the supervision of animal welfare during the trial. The duration of the period of observation should be stated.

6.2.6 Information on unintended effects, whether harmful or not

Information on any side effects (i.e. expected adverse effects), or adverse effects to administration of the test product in treated animals during or following the administration of the product should be provided. This should include, as relevant, information on any rescue procedures to be administered or procedures to be followed in the case of unintended effects.

6.2.7 Information on the withdrawal period (in the case of veterinary medicines used in food-producing animals)

According to Article 115 of Regulation 2019/6, unless the test product has a marketing authorisation already (in which case the authorised withdrawal period(s) will normally apply), the withdrawal period for the test product shall be at least 1.5 times that indicated for an existing target species, and will take into consideration the specific requirements set by that Article. Where the test substance contained in the veterinary medicine is not authorised for food-producing animals, but a maximum residue limit (MRL) exists for the species intended for trial, the withdrawal period shall take into account the time needed for residues to deplete to below the MRL or reference values.

However, depending on the nature of the test product, the dosage being administered and the route of administration, the proposed withdrawal period should include an appropriate safety

factor in order to ensure the safety of foodstuffs for the consumer. The proposed withdrawal period(s), as well as the calculations used to derive them, should be provided.

Where no MRL exists for the test product, it will generally be necessary to ensure that foodstuffs from treated animals are excluded from entry into the food chain.

6.3 Animals to be used

The species of animals to be used should be indicated. Where relevant, information to characterise specific sub-populations should also be given (e.g. puppies >12 weeks of age; in-calf heifers, etc.).

6.3.1 Consent of animal owners

In the case that the animals being used in the trial are not the property of the applicant or sponsor, confirmation that the informed consent of the owners of the animals used in the trial will be obtained and documented is required.

6.3.2 Information on categories of animals to be used

Justification for the use of animals taken from the wild, or for the use of stray or feral animals, or the use of animals of an endangered species is required.

Where a trial animal might be re-used from a previous trial, an appropriate justification should be provided.

6.3.3 Fate of trial animals

Information on the fate of trial animals at the end of the trial should be given (e.g. whether they will be euthanised, returned to the flock, slaughtered in a licensed abattoir, etc.).

7 SECTION D – DECLARATION AND UNDERTAKING

The declaration and undertaking must be signed by the applicant (i.e. the investigator, or the trial director on behalf of an applicant company).

In the event of the trial licence being granted, by signing the declaration and undertaking, the signee is assuming the responsibility for the overall implementation and compliance of the trial with the legislation and with respect to fulfilment of the conditions and obligations as set out in the declaration and undertaking. They are also confirming they will comply with any conditions which may be included in the licence itself, including ensuring the security of any test products (those that do not have a marketing authorisation granted by the HPRA or European Commission) which must be used only for the purpose of the trial.

8 MAKING AN APPLICATION

A clinical field trial licence application consists of the following:

- a complete and signed clinical field trial application form
- a detailed trial protocol
- when conducted, the ethics review application, supporting institutional ethics committee approval information and any associated documentation in which queries have been raised and addressed (where applicable)
- certificate confirming composition of any test product that does not have an existing marketing authorisation, as well as accompanying statements regarding GMOs, TSE and extraneous agents
- summary data regarding the safety and risk profile of any test product that does not have an existing marketing authorisation
- a CV for the person with responsibility for the conduct of the trial
- proof of payment of the appropriate fee

A covering letter may also be provided. This is not a requirement; however, it should be provided in situations where the trial application is urgent.

General queries in relation to making an application should be addressed to vetinfo@hpra.ie.

9 ADMINISTRATIVE DETAILS

Due to the possible sensitive nature of information contained in clinical field trial applications, the HPRA provides a secure online system to enable submission of applications and data. This system is known as CESP – the Common European Submission Platform. The HPRA Veterinary Sciences Department can provide more information on this submission route. Applications can also be submitted by standard email to submissions@hpra.ie.

If the application cannot be submitted electronically, applications will be accepted in hard copy by post. Hard-copy applications that arrive by post must be electronically scanned by the HPRA resulting in additional processing time for evaluation.

Send postal applications to:

Receipts and Validation Section
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2

Applications that do not include the necessary information are not eligible for HPRA evaluation. If an application is incomplete, the applicant will be notified as quickly as possible via the email address on the application form.

Queries in respect of application requirements or communications relating to clinical field trial applications submitted can be made by telephone, fax, email or by post to the address below:

Veterinary Sciences Department
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
D02 XP77
Tel: +353 1 676 4971
Email: vetinfo@hpra.ie

Fees:

Clinical field trial applications are subject to fees and the evaluation process will not begin without the appropriate fee. Please consult www.hpra.ie for the relevant fees.

The HPRA is obliged to consult with the DAFM before granting a licence for a clinical field trial. It is suggested that at the same time as the application is being made to the HPRA, a copy of the application is submitted to the DAFM at:

Veterinary Medicines Section
Department of Agriculture, Food and the Marine,
Backweston Administration Building Reception
Stacumny Lane,
Celbridge,
Co. Kildare
W23 X3PH
Email: veterinary.medicines@agriculture.gov.ie