

GOOD CLINICAL PRACTICE FOR THE CONDUCT OF CLINICAL TRIALS ON VETERINARY MEDICINAL PRODUCTS IN THE EUROPEAN UNION

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GOOD CLINICAL PRACTICE FOR THE CONDUCT OF CLINICAL TRIALS ON VETERINARY MEDICINAL PRODUCTS IN THE EUROPEAN UNION ⁵

FOREWORD

The objective of this document is to provide guidance for practice on the conduct of clinical trials on veterinary medicinal products in the European Union. It is directed to all those involved in the conduct of such trials and is intended to ensure that those trials are conducted and documented in accordance with Part 4, Chapters II and III, and Parts 8 and 9 of the annex to Directive 81/852/EEC as amended.

Pre-established systematic written procedures for the organisation, conduct, data collection, documentation and verification of clinical trials are necessary to establish the validity of data and to improve the ethical, scientific and technical quality of trials.

The welfare of the trial animals is ultimately the responsibility of the investigator for all matters relating to the trial. All investigators must demonstrate the highest possible degree of professionalism in the observation of animals in the trials and the reporting of such observations. Independent assurance that the trial animals and the human food chain are protected should be provided by the authorisation procedure of the competent authority and the procedure for informed consent of the owner of the animals.

Safety and preclinical trials, including pharmacokinetic studies, are not included in the scope of this document since guidelines are already in existence. However, in those Member States where it is required, data derived from such trials must be submitted to the relevant competent authority in order that the clinical trial or series of trials may be properly authorised prior to commencement.

In conducting clinical trials, due regard must be taken of the possible effects of the product on the environment, on residues in the produce of treated animals, and the eventual fate of animals used for food consumption.

1. RESPONSIBILITIES

Sponsor

1. Each Sponsor will establish detailed Standard Operating Procedures (SOP) for the elements contained in the protocol.
2. With regard to trial protocols the recommendations contained in Chapter 2 of this guideline will be carefully followed during their construction.
3. Both the Sponsor and Investigator/Site Supervisor will sign the protocol as an agreement of the details of the clinical trial. Any amendments to the protocol must have the signed agreement of both Sponsor and Investigator/Site Supervisor.

⁵ All studies started after 1 July 1995 shall be carried out in accordance with this note for guidance

4. Furthermore, the Sponsor will:
- a) select the Investigator/Site Supervisor, and assure his/her qualifications, assure his/her availability for the entire duration of the study, ensure that he/she agrees to undertake the study as laid down in the protocol, according to this note for guidance of practice, including the acceptance of verification procedures;
 - b) inform the Investigator/Site Supervisor of the relevant chemical/pharmaceutical, toxicological and clinical details as a prerequisite in planning the trial;
 - c) submit notification/application to the relevant authorities where required;
 - d) provide the investigational medicinal product(s) in suitable packaging and labelling, in conformity with the principles of GMP, and in such a way that any blinding procedure is not invalidated. The labelling should include the words "For Veterinary Clinical Trial Only";
 - A sample of each batch should be kept for reference for one year after the end of shelf life.
 - Records of the quantities of medicinal product(s) supplied should be maintained with batch/serial numbers. Certificates of delivery of the medicinal product(s) signed by the investigator must detail the method and place of storage to identify the exclusive use of the product(s) in the trial. It will subsequently be used to account for unused supplies.
 - Appropriate recommendations for disposal of unused supplies should be given.
 - e) appoint appropriately qualified and trained Monitor(s);
 - f) report all suspected Adverse Drug Reactions (ADR) in accordance with relevant requirements;
 - g) inform the Investigator/Site Supervisor of any critical information that becomes available during a trial and ensure that when required the relevant authority is notified;
 - h) ensure that a final trial report suitable for regulatory purposes is prepared whether or not the trial has been completed;
 - i) provide adequate indemnity for the Monitor and Investigator/Site Supervisor and compensation for animal owners in the event of injury or death of the animal or loss of productivity related to the trial.

Monitor

The Monitor will be the principal communication link between the Sponsor and the Site Supervisor/Investigator and will:

1. help the Sponsor to select the Site Supervisor/Investigator;
2. work according to predetermined SOPs, visit the Investigator\Site Supervisor before, during and after the trial to control adherence to the protocol and ensure that all data are correctly and completely recorded and reported and that informed consent is being obtained and recorded from the owner(s) of trial animals prior to including his/her animals;
3. ensure that the trial site has adequate space, facilities, equipment, staff, and that an adequate number of trial animals is likely to be available for the duration of the trial;

4. ensure that trial staff have been adequately informed about the details of the trial;
5. be reasonably available to the Investigator/Site Supervisor for consultation, in person or via telephone, facsimile machine, telex, electronic mail etc.;
6. check that the storage, dispensing and documentation for the supply of investigational medicinal product(s) are safe and appropriate, and ensure that any unused medication is returned by the owner(s) to the Sponsor or to an approved site;
7. submit a written report to the Sponsor at agreed regular intervals to include the reporting of all telephone calls, visits, letters and other contacts with the Investigator/Site Supervisor (audit paper trail concept). These reports will form part of the trial documentation.

Investigator/Site Supervisor

The Investigator/Site Supervisor will:

1. agree the protocol with the Sponsor via the Monitor and confirm in writing that he/she will work according to the protocol, and adhere to this note for guidance;
2. submit an up-to-date curriculum vitae and other credentials to the Sponsor;
3. obtain informed consent from the owners of trial animals. The animal owner must receive written information from the Investigator/Site Supervisor in advance;
4. provide all relevant information to all staff members involved with the trial or with other elements of the management of the trial animals. This should include the local veterinary surgeon that normally attends the animals;
5. ensure that the investigational medicinal product(s) are correctly stored and safely handled. Ensure investigational medicinal products are dispensed to trial subjects in accordance with the protocol and to maintain a full inventory of receipt, usage and remaining stocks. At the end of the trial it must be possible to reconcile delivery records with those of usage and returns including accounting for any discrepancies;
6. manage any code procedure and documentation (e.g. randomisation envelopes), with due professional care, and ensure that any treatment code is only broken in accordance with the protocol and with the Sponsor's/Monitor's knowledge and consent;
7. collect and record data in accordance with protocol requirements;
8. in the case of ADRs immediately notify the Sponsor and Monitor and, where required, relevant authorities;
9. make all data available to the Sponsor/Monitor for the purposes of validation;
10. ensure the accuracy of any report drafted for him/her;
11. forward signed Record Sheets to the Monitor. Collaborative Investigators and those responsible for the analyses (including statistical analyses) and the interpretation of the results should also sign the relevant Record Sheets. Where appropriate, all practice records will be clearly marked that the animal(s)/owner is participating in a clinical trial;
12. observe the following points particularly related to animal care:
 - a) the Investigator/Site Supervisor will be expected to give assurance that he/she has sufficient time to devote to the study, access to adequate staff and facilities for the

conduct of the study, and that suitable equipment is immediately available in case of emergency;

- b) the Investigator/Site Supervisor is responsible for animals under his/her care for the purpose of the trial and, where the Investigator/Site Supervisor is not a veterinary surgeon, will ensure that their care is maintained during and after the trial. The local veterinary surgeon should be kept informed.

2. GUIDE FOR THE CONDUCT OF CLINICAL TRIALS

A well designed trial relies predominantly on a thoroughly considered, well structured and complete protocol which should be completed and approved by the Sponsor and Investigator/Site Supervisor before the trial is initiated.

The protocol will, where relevant, contain the information given in the following list of items, or this list should at least be considered whenever a trial is contemplated and reasons for any omissions given.

General information

1. Title of the study.
2. Each study will be given an identifier unique to the Sponsor.
3. The expected names and contact points of the Investigators responsible for the trial; the expected names of other possible participants and their professional background (e.g. veterinarian, biochemist, parasitologist, experimental animal attendant, statistician etc.) should also be made clear.
4. The name and any contact point of the Sponsor.
5. If known, the identity of the farm/department/group of veterinary practices where the trial will take place (affiliations, addresses).

Justification and objectives

1. The objective in conducting the study must be clearly established.
2. The essentials of the problem itself and its background, referring where appropriate to relevant literature.

Schedule

1. Description of the schedule of the trial, i.e. its expected date and time of commencement, investigation period, observation period and termination date where known.
2. Justification of the schedule, e.g. in the light of how far the safety of the medicinal product has been tested, the time course of the disease in question and expected duration of the treatment.
3. Justification of the withdrawal period before slaughter etc. Even if the post-medication period of observation of the live animal is in excess of this period, a withdrawal period must be proposed for all food producing animals in the trial.

Design

1. Specification of the type of trial, e.g. controlled study, pilot study.
2. Description of the randomisation method, including the procedures to be adopted and practical arrangements to be followed.
3. Description of the trial design (e.g. parallel groups, cross-over design) and the blinding technique selected.
4. Specification of other bias reducing factors to be implemented.
5. Description and justification of the experimental unit(s).

Animal selection

1. Specification of the type of animal to be used, including species, age, sex, breed, category, reproductive status, prognostic factors etc.
2. The housing and management of the animals.

Inclusion/exclusion criteria

1. Provision of a clear statement of diagnostic admission criteria.
2. Detailed listing of the criteria for inclusion and, if possible, pre-admission exclusions and post-admission withdrawals of animals from the trial.

Treatments

1. Clear, precise and detailed identification of the product(s) to be used. These should be fully formulated products likely to be proposed for marketing. There should be a justification of the doses to be used.
2. Description of treatment applied to the control group(s) or for control period(s) (placebo, other products, vehicle only, no treatment etc.).
3. Route of administration, dosing schedules, treatment period(s) for the test product(s) containing the active substance under investigation and for the comparative product(s).
4. Rules for the use of concomitant treatment.
5. Measures to be implemented to ensure the operator's safety whilst handling the test products prior to and during administration.
6. Measures to promote and control close adherence to the prescribed instructions/ordinances (compliance monitoring).

Assessment of efficacy

1. Definition of the effects to be achieved before efficacy can be claimed.
2. Description of how such effects are measured and recorded.
3. Times of, and periods between, observations and concomitant recording of the effects.
4. Description of special analyses and/or tests to be carried out with times of sampling and interval before analysis/test.

Adverse events

1. Methods of recording and monitoring suspected adverse events.
2. Provisions for dealing with such events, e.g. treatment, changes to method of administration.

3. Information on where the trial code will be kept and how it can be broken in the event of an emergency.
4. Details for the reporting of suspected ADRs and all side effects, particularly the name of the individual designated to receive such reports.

Operational matters

1. A detailed plan should be drawn up of the various steps and procedures necessary to control and monitor the trial most effectively.
2. Definition of an instruction for anticipated deviations from the protocol.
3. The duties and responsibilities of the investigation team and their co-ordination.
4. Instructions to staff, including a trial description.
5. Addresses, telephone numbers etc. enabling any staff member to contact responsible members of the investigation team at any hour.

Handling of records

1. Procedures for handling and processing the records of various effects, including suspected ADRs, relating to the use of the product(s) under study should be defined.
2. Procedures for the maintenance of all the records for each individual (or test group) within the trial must be available. If animals are treated individually then the records must permit the identification of the individual concerned.
3. A copy of the test animal record sheet should be included.

Evaluation

1. Definition of the measure of test animals' response, e.g. a scoring system, and other measurements made in order to evaluate the clinical response.
2. Definition of the methods of computation and calculation of the effect of the medicinal product.
3. Description of how to deal with and report on animals withdrawn or otherwise removed from the trial.

Statistics

1. A thorough description of the statistical methods to be employed.
2. The planned number of animals to be included in the trial(s) and the reasoning for the choice of sample size, including reflections on (or calculation of) the power of the trial and the clinical justification, should be provided.
3. Description of the statistical unit/experimental unit.
4. The level of significance to be used.

Supplements

The protocol should comprise a comprehensive summary and relevant supplements (e.g. information to the owners of the animals, informed consent form, instructions to staff, description of special procedures).

References

A list of relevant literature, referred to in the protocol, must be included.

3. DATA HANDLING

General

1. The person recording an observation will sign and date it or, in the case of the supervisor, each page of observations.
2. Data should be recorded on pre-established durable recording sheets. Record sheets should be diligently completed indelibly in ink or ball pen, with all the data points recorded as required in the protocol. However, when additional observations are considered necessary by the Investigator/Site Supervisor they should also be recorded on the record sheet together with a comment as to their perceived significance.
3. Units must always be stated, and transformation of units must always be indicated and documented.
4. All corrections on a record sheet and elsewhere in the raw data must be made by drawing one straight line through the erroneous values, which should still be legible. The correct data must be inserted with date and signature or initials, if possible with reasons for change. An alternative would be to use a correction form.
5. Laboratory values should always be recorded on a record sheet or attached to it. Values outside an accepted reference range must be certified by the Investigator. Normal reference values for the laboratory should be included.
6. If data are entered directly into a computer there will be adequate safeguards to ensure validation including a signed and dated print-out. In this case the electronic record or the print-out may be referred to as Raw Data.
7. If, for example, during (direct) data entry, data are transformed by coding, the transformation must be documented.
8. For electronic data processing only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions.

Investigator

The Investigator guarantees the correctness and completeness of the data with a signature and date on each record sheet.

Sponsor

1. The Sponsor will use properly documented and validated data entry handling and analytical systems/programmes.
2. The Sponsor will be able to identify each experimental unit (animal or group of animals) by unambiguous means.
3. SOPs will include systems for dealing with electronic data.
4. The Sponsor will ensure the greatest possible accuracy when converting data electronically. It should be possible to obtain a data print-out which can be compared with the raw data.
5. Computer data systems will be designed to allow correction after loading but the correction must be documented and traceable by date and identity of the person making the correction.

6. The Sponsor will maintain a list of persons authorised to make corrections and protect the data by appropriate password systems.

Archiving of data

1. Wherever possible, the investigational centre should forward all raw data to the Sponsor for archiving. Where this proves impractical, the investigational centre must ensure adequate archive facilities and forward copies to the Sponsor. The Sponsor must ensure that the Trial Master File contains a listing of all information which is available and where it can be found.
2. The Protocol, documentation (including data on Suspected Adverse Events), approvals and all other documents related to the trial will be retained by the Sponsor in the Trial Master File for a period of five years after the product is no longer authorised.
3. All data and documents will be made available for inspection if requested by relevant authorities.

4. STATISTICS

1. Access to biostatistical competence will be mandatory. Where and by whom the statistical analyses are carried out will be the responsibility of the Sponsor.
2. The type of statistical analysis to be used will be specified in the protocol and any subsequent deviations from the plan will be described and justified in the final trial report. Calculations and analyses will be confirmed by a named statistician.
3. The statistician and the Monitor will ensure that the data are of high quality at the point of collection and subsequent processing. The statistician will be expected to ensure the integrity of subsequent data processing by using proven and scientifically recognised statistical procedures. An account will be made of missing, unused and spurious data during statistical analysis. All exceptions will be documented for further review if required.

5. DATA VERIFICATION

1. Procedures for data verification will be applied to each stage of data collection, recording and processing.
2. The Sponsor/Monitor will be expected to perform the following functions before, during and after the study:
 - a) Monitor at the trial site to ensure that the investigational product(s) and record keeping are being handled correctly and that Adverse Events are properly recorded and reported.
 - b) Account for the supply and use of investigational and reference substances.
 - c) Monitor the Investigator's procedures and facilities in accordance with the Protocol and SOPs. Any deviations will be documented and justified.
 - d) Verify data through each processing procedure.
 - e) Account for all relevant trial documents and have them available for future audit if required.

- f) Check all statistical methods, calculations and conclusions. Reference to validated statistical software will be acceptable.
- g) Ensure that the Final Trial Report is in accordance with the methods used in the study, and the reported results and suspected Adverse Events reflect accurately the recorded data.
- h) Report all discrepancies found during data verification.
- i) Check data archives for ability to retrieve selected data.
- j) Ensure that all the above elements are available for audit by an independent body, should this be required. Laboratory and other trial procedures may also be inspected.

6. FINAL TRIAL REPORT

As described in Chapter 1 of this document it is the responsibility of the Sponsor to prepare a Final Trial Report (FTR) for regulatory purposes whether or not the trial has been completed as planned. The FTR will form the primary record of clinical observations referred to in the annex to Directive 81/852/EEC as amended (Part 4, Chapter III, Section 2.1 and Part 9, Sections B and C). The structure of the FTR will follow the format of the trial protocol as defined in Chapter 2 of this document, and a copy of the trial protocol will be appended to the FTR.

In accordance with the above-mentioned Directive the FTR will include relevant information from the following list:

1. the names of all people involved in conducting the trial, including the Investigator, Monitor, Site Supervisor, Technical Assistants, Statisticians and Veterinary Surgeons;
2. the address of the premises at which the trial was conducted (e.g. farm, institute or veterinary practice) and the name(s) of the owner(s) of the animals. In the case of a trial involving companion animals, it will only be necessary to use suitable practice reference codes on the Record Sheets to identify the animal owners;
3. details of animal management including the composition of feed and the nature and quantity of any additives in the feed;
4. disease history, relevant to the condition under investigation, especially in the case of specific disease problems associated with a farm unit;
5. diagnosis of the disease being treated, including a description of the clinical signs according to conventional criteria. Reports from laboratory or post-mortem examinations used to identify the condition will be summarised in the FTR, and appended;
6. the precise identification of the clinical trial formulation used in the trial including lot or batch numbers;
7. the dosage of the medicinal product, method, route and frequency of administration and precautions, if any, taken during administration;
8. the duration of treatment and period of subsequent observation;
9. a full description of methods used and observations and measurements made;

10. a full description of animals involved in the trial, including numbers of each sex in each treatment group, and details of randomisation and blocking techniques used in the allocation of animals to treatment groups;
11. full information on any animal withdrawn from the study;
12. details of any other medicinal product(s) which was (were) administered during the trial, either prior to, during or after the test product, and details of any interactions observed;
13. a full description of the results of the trial whether favourable or unfavourable, including tables of all data recorded during the trial. Reports from laboratory or post-mortem examinations conducted during the trial will be appended to the FTR;
14. details of any suspected Adverse Drug Reactions or other Adverse Events occurring during the trial and any measures taken as a consequence;
15. any effects on animal performance (e.g. egg laying, milk production, or reproductive function);
16. a conclusion based on results from each individual case or treatment group as appropriate;
17. a summary of the trial including a statement of the objective, the materials and methods, the results, and the main conclusions that can be drawn from the results.

The FTR will be signed by the Sponsor and the trial Monitor indicating that it represents a complete and accurate record of the clinical trial.

GLOSSARY

Adverse Drug Reaction (ADR): A reaction which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

Adverse Event (AE): Any undesirable experience occurring to a test animal during a clinical trial whether or not considered to be related to the investigational product.

Audit (of a trial): A comparison of raw data and associated records with the interim or final report in order to determine whether the raw data have been accurately reported, whether testing was carried out in accordance with the trial protocol and standard operating procedures, to obtain additional information not provided in the final report, and to establish whether practices were employed in the development of data that would impair their validity. The audit must be conducted either through an internal facility at the Sponsor's, but independent of the units responsible for clinical research, or through an external contractor.

Clinical Study: A number of clinical trials conducted to a similar protocol.

Clinical Trials: Systematic studies in target species or in the particular categories of such animals, in order to establish the therapeutic effects which could include confirmation of the pharmacodynamics and/or to monitor any suspected adverse response from the use of veterinary medicinal products.

Documentation: All records in any form (including documents, magnetic and optical records) describing methods and conduct of the trial, factors affecting the trial, and the action taken. These include protocol, raw data, Investigator's reports, Monitor's reports, letters, biochemical reference ranges, final trial report, etc.

Final Trial Report: A complete and comprehensive description of the trial after its completion prepared by the Sponsor, Investigator or Monitor, including a description of material and methods, a presentation and evaluation of the results, statistical analyses and a critical clinical and statistical appraisal.

Informed Consent: The confirmation of an owner's willingness to participate in a particular trial. This confirmation should only be sought after information has been given about the owner's rights and responsibilities, about the risk and inconveniences related to the investigation and the objectives and benefits thereof. In the case of food producing animals, the owner shall be informed in writing of the consequences of participation in the trial, for the subsequent disposal of treated animals or for the taking of foodstuffs from treated animals. A copy of this notification countersigned and dated by the animal owner or the Investigator shall be included in the trial documentation.

Investigational Centre: A commercial or scientific body to which a Sponsor may transfer some tasks and obligations. Any such transfer shall be in writing and shall describe each of the obligations assumed by the Investigational Centre.

Investigational Product: Any active ingredient, medicinal product or placebo being tested or used as a reference in a clinical trial.

Investigator: The person responsible for the practical performance of a trial and for the health and welfare of the animals during the trial.

The Investigator is:

- appropriately qualified;

- experienced in the performance of clinical trials;
- familiar with the background to and the requirements of the study.

Trained technical assistants may help in data collection and subsequent processing.

Monitor: A person appointed by the Sponsor or Investigational Centre to be responsible to the Sponsor or Investigational Centre for the monitoring and reporting on progress of the trial and for verification of data. The Monitor must have qualifications and experience to enable a knowledgeable supervision of the particular trial.

Protocol: A document which states the rationale and objectives of the trial with the conditions under which it is to be performed and managed. A list of items to be included in the protocol is given in Chapter 2 of this note for guidance.

Raw Data: The record of the original clinical and laboratory findings during a trial or certified copies of the same.

Record Sheet: A record of the data and other information on each experimental unit as defined in the protocol. These shall be Individual Record Sheets in the case of individual treatments and Collective Record Sheets in the case of collective treatment. The data may be recorded by any means which ensures accurate input and presentation and allows verification.

Regulatory Authority: An independent or governmental body whose responsibility is to verify that the rights and integrity of trial animals and their owners are protected, and thereby provide public reassurance as to the welfare and well-being of animals receiving Investigational Products, to determine the safety of products entering the food chain derived from trial animals, and to ensure safety to the operator and the environment from the use of Investigational Products.

Site Supervisors: Investigators responsible for an individual trial at a single location.

Sponsor: An individual or an organisation which takes responsibility for the initiation, management and financing of a clinical trial. When an Investigator independently initiates and assumes responsibility for a study that may subsequently become a part of an application for a marketing authorisation, the Investigator then also assumes the role of the Sponsor.

Standard Operating Procedures: Detailed written instructions describing the practical procedures, test methods and management operations to be performed or followed, precautions to be taken and measures to apply.

Trial Animal: A farm or companion animal, or groups of the same, included in a clinical trial.

Trial Master File: Document comprising protocol, raw data, original recordings from automated instruments, laboratory notes, records or telecons, documentation and final trial report.

Verification/Validation of Data: The process carried out to assure that the data contained in the final trial report match original observations. These procedures may apply to raw data, hard copy or electronic reports, computer print-outs and statistical analyses and tables.