GOOD CLINICAL PRACTICE

The VICH guideline for clinical studies in veterinary medicinal products

An investigator's handbook

Health for Animals
global animal medicines association

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Foreword

This handbook is aimed at anyone involved in the implementation of clinical studies, but more particularly at clinical investigators, and should be read in conjunction with VICH GL9 Good Clinical Practice.

Indeed, in the final stretch, after several years of research, financial efforts and manpower involvement, when the R&D process is nearly at its end, the whole team involved in the project rely on the last link in the chain: the clinical investigator.

Because of the key role they have to play and because this role must be played in accordance with a stringent partition (Good Clinical Practice), it is essential that investigators are aware of the implications of the task they have to fulfil.

The VICH guidance document represents the current best judgement of the relevant regulatory authorities on Good Clinical Practices (GCP). It does not create or confer rights for or on any person and does not operate to bind the relevant regulatory authorities or the public. An alternative approach may be used if such an approach satisfies the applicable regulatory requirements. If a sponsor chooses to use alternative procedures or practices, discussion with the regulatory authority is advised.

When a guidance document states a requirement imposed by law, the requirement is law and its force and effect are not changed in any way by virtue of its inclusion in the guidance document.

The purpose of this handbook is to provide a comprehensive understanding of clinical studies, to help the investigators to respect their commitments with the extra rigour and the extra discipline required.

Introduction

The objective of this handbook is to provide guidance on the design and conduct of all clinical studies of veterinary medicinal products in the target species.

It is directed at all individuals and organizations involved in the design, conduct, monitoring, recording, auditing, analysis and reporting of clinical studies in target species and is intended to ensure that such studies are conducted and documented in accordance with the principles of Good Clinical Practice (GCP).

Good Clinical Practice is intended to be an international ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analyzing and reporting clinical studies evaluating veterinary products. Compliance with this standard provides public assurance about the integrity of the clinical study data, and that due regard has been given to animal welfare and protection of the personnel involved in the study, the environment and the human and animal food chains.

The VICH "guideline" has been developed under the principles of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) and provides an international standard to facilitate the mutual acceptance of clinical data by regulatory authorities.

This guidance should be followed when developing clinical study data that are intended to be submitted to regulatory authorities.

The ultimate aim of this handbook is to promote GCP implementation and to give investigators a clear definition of their role in clinical studies.

This handbook provides investigators with recommendations and principles on the way they must work with the sponsor to produce accurate data, to protect public health, the environment and to respect animal welfare.

Part I: Understanding Clinical Studies

Definition of clinical studies

There is a wide range of interpretation given to the terms clinical studies amongst companies, but also authorities.

However, when referring to the GCP concept, only some studies are eligible to the clinical studies definition.

Therefore, in this manual, when speaking of clinical studies, we will retain the most common definition, which springs from the European legislation, in particular Directive 92/18 and the VICH guideline on GCP for the conduct of clinical studies for veterinary medicinal products.

Clinical studies are designed either to adapt the effective dose to field circumstances (dose-confirmation study) or to verify the effectiveness and acceptability of the product under normal conditions of use.

Thus, clinical studies are performed when the efficacy and safety of the product have already been demonstrated under specific and highly controlled circumstances.

During clinical studies, the efficacy of the drug under test is assessed on diseased animals, and a comparison is made with the outcome of control animals which are either left untreated (negative control) or treated with an authorised medicinal product of comparable therapeutic value (positive control).

Clinical studies are usually extensive and involve a wide range of animals of different age, sex and breed maintained under diverse husbandry conditions.

Rationale

When carrying out a clinical study, a company wants to determine the efficacy of the product under test. For this purpose, the investigational veterinary product can be compared to a reference product, of which the efficacy and therapeutic value are known. Where no reference product is available, untreated animals can be compared with animals treated with the investigational veterinary product. Nevertheless, in both cases, the purpose is to find a statistical answer to the question: clinically, how do the treatments compare in terms of specified parameters?

To answer this question, the study must be properly designed to ensure that any variations recorded are the sole result of differences between treatments.

Among the parameters studied, particular attention must be paid to extraneous factors which could be recorded and thus bias the outcome of the study. In particular, systematic errors (also called bias) occurring non-randomly and affecting the average of the parameters recorded, are a major concern. Usually, the most important source of bias is that related to the investigator.

Unfortunately, statistical methods are inefficient in evaluating the impact of bias, which therefore has to be identified and then to be reduced or controlled through specific techniques, such as standard operating procedures (SOPs). These provide a detailed and consistent framework of what has to be done and how. Other techniques such as blinding, randomisation and control groups will also help to reduce the incidence of bias. In particular, randomisation within a study will help to convert any remaining bias into random error.

Extracts of VICH guideline 9 on GCP have been added to this handbook but for a full in-depth knowledge of this document reference to the appropriate sections should be made.

Nevertheless even for a bias-free study, random errors, which affect the variance and not the average of the variables recorded, still occur. One purpose of clinical study is to assess the significance of this random variability.

To enable a statistically significant analysis to be conducted, the sample of clinical cases used in the study must have an appropriate size and be representative of the whole population. The sample size is determined before the study is undertaken and depends on the statistical procedure that will be used, on the variability of the parameters to be measured (this variability may be estimated during a pilot study phase) and on the expected difference between the treatment groups.

When recruiting clinical cases, providing the treatment and recording the data, the investigator should always keep in mind that work not conducted in the prescribed way (i.e. according to the protocol) reduces the sample size, which becomes less representative. Moreover, it leads to a study with reduced significance and to delays and potential difficulties in obtaining marketing authorisation. In certain cases the study might have to be repeated as the protocol was not followed. And this will be a waste of time and resources.

The purpose of a clinical study is to get a clinically relevant statistical answer.

Design of the study

A good clinical study must accurately evaluate a product so that the results obtained can be extrapolated to the whole target population. Study design is the responsibility of the sponsor. However, the investigator needs to be comfortable with the approach.

A study is usually performed in several centres (MULTI-CENTRED study), reflecting the diversity of the target population. For further guidance on statistics, reference should be made to the CVMP GL on Statistical Principles.

Three principles must be met when designing a study:

- **COMPARISON** – the investigational medicinal product must be evaluated in comparison to a *CONTROL* (either a reference product or a placebo).

- **CAUSALITY** – the groups to be compared must only differ on the treatment received and they must be comparable at inclusion (*RANDOMISATION*) and during the study (*BLINDING*).

- **SIGNIFICANCE** – the differences observed between the groups must be statistically significant, i.e. for the differences to be attributed to the treatment, the difference from the sampling fluctuation must meet the statistical significance standard.

STUDY CONTEXT

Depending on the aim of the study, it can be classed into one of the following three categories:

1. Confirmatory Study

These studies can concern dose determination studies and dose confirmation studies as well as controlled field studies.

2. Exploratory Study

The rationale and design of these studies often rests on earlier clinical work carried out in a series of exploratory studies. They are precursors to confirmatory studies.

3. Composite Study

These studies may have the opportunity to subject the data to further exploratory analyses, which may serve to explain and support the study findings and to suggest further hypotheses for research. The protocol should make a clear distinction between those aspects of the study, which are confirmatory, and those, which are exploratory.

EXPERIMENTAL UNIT

In veterinary clinical studies there are a variety of situations where the experimental unit is not the animal but the pen, room, pasture or litter, as well as an udder quarter for milking cows. For example dogs and cats tend to be presented in a veterinary surgery singly or may be group housed in a kennel or cattery. Chickens are generally housed in groups of hundreds (layers) or many thousands (broilers). Pigs on the other hand, may be seen singly (sow or boar), as a litter (sow plus 10-12 piglets), a weaner pool (25-30) or a fattening group (pens of 10-40). A fish tank or cage can also constitute an experimental unit.

The experimental unit should be clearly specified in the protocol, since it is essential to the sample size calculation.

SAMPLE SIZE

The number of experimental units in a clinical study should always be large enough to provide a reliable answer to the question asked. The number is usually determined by the primary objective of the study. If the sample size is determined by other means, then this should be made quite clear and justified.

The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculation.

Sample size calculations should refer to the number of experimental units required for the primary analysis.

FIELD STUDY GOLD STANDARD

- Multi-centred
- Randomised
- Controlled
- Blinded

1 – MULTICENTRED STUDY

It can be advantageous to implement a clinical study in several centres. So, the diversity of breeds, of husbandry systems, of pathogen susceptibility is reflected as accurately as possible. Furthermore when criteria are partially subjective (e.g. clinical scores) and not precisely reproducible, a multi-centred study enables the enrolment of investigators from various areas, cultures or habits so that this sample of practitioners will be more representative of the whole population.

2 – CONTROLLED STUDY

The ultimate aim of a study is to assess the efficacy of the product under test. Therefore, it is essential to have a reference, i.e. a control group, which is a group of animals treated with another compound, and/or a group of animals receiving no treatment or a placebo.

Negative control group

The animals of the negative control group are left untreated or receive a placebo. The placebo is an inactive imitation (usually the vehicle) of the investigational veterinary product tested, which enables the assessment of possible self-cure of a disease or extraneous factors that might affect the evaluation of the response to a treatment.

PLACEBO EFFECT OR ACTIVE PLACEBO

Cats were treated in blind conditions with either a NSAID or a placebo. Through a questionnaire their owners were asked if they noticed any side effect, including digestive disorders (diarrhoea, vomiting). The results were as follows:

	NSAID	Placebo
% side effects	2.26	21.9

The percentage of reported side effects with the placebo is astonishingly high. It is a very good example of psychological response, so-called placebo effect. Or was it that the placebo was not fully inactive?

Although the placebo effect might be less relevant in veterinary medicine, it can still play a role when the clinical investigator or the owner of the animal is required to evaluate some parameters such as appetite, general conditions, side effects...

Furthermore, through the placebo method, the products can be blinded, so that animals of both groups are handled similarly.

The main advantage of a negative versus a positive control group is that with a negative control group fewer cases are needed, because the expected difference between the treatments is higher and thus easier to detect. However, it is sometimes difficult, impossible or unethical to use a negative control group. It is contrary to the concept of Good Veterinary Practice for a veterinary surgeon to deny appropriate treatment to an animal under his care, especially in life-threatening conditions. Also, because of the potential economic losses, farmers may be reluctant to give their food-producing animals a placebo or no treatment at all.

Positive control group

A comparison can be performed using a positive control group, which is given a registered reference product. This product is chosen by the company (the sponsor), it is the same for the whole study, and it is indicated for the disease and the target species claimed for the tested drug. This method is ethically the most satisfactory and should be used in any situation where animals require a treatment (e.g. antibiotics).

Historical control group

The group of treated animals is compared to a similar group previously treated or untreated, or to a fictitious group when the prognosis is predictable (milk fever). This method requires few cases but the interpretation is very approximate because the groups are seldom comparable. In particular, animals of the historical group might have been included or evaluated according to a different protocol.

Own control group

After a period of wash out (i.e. a waiting period ensuring complete elimination of the drug), the animal will be its own control. It thus receives each of the two products during two successive periods or in two locations of the body for topical preparations. This approach is rare and limited to rather unprogressive diseases or some skin diseases.

However, in some cases, because of the field conditions, it can be difficult or impossible to perform a controlled study. In particular, for vaccines (unpredictable disease and/or of low incidence); for diseases of companion animals where a single treatment is available and when the majority of animals enrolled in the study have already and unsuccessfully received the reference product; or for diseases where there is no reference treatment.

3 – RANDOMISED STUDY

In a controlled study, the allocation of animals to the treatment groups must be randomised. Thus, each animal is as likely to be allocated to the treated group as to the control group. Otherwise one might be tempted, as an example, to systemically give the new treatment (assumed to be more effective) to the most severely affected animals.

> Randomisation ensures that on average the groups are initially equal.

When randomising, parameters such as investigator, extent of the disease, breed, sex weight and age of animals, have to be taken into account and a balance has to be kept in the distribution between the different treatment groups. As a consequence, it increases the power of the study. However, stratification on many factors makes the randomisation much more complex and is not always compatible with the field conditions.

The randomisation schedule of a clinical study documents the random allocation of treatments to study animals. In the simplest form it could be a sequential list of treatments (or treatment sequences in a cross over study) or corresponding codes by animal number. Different study designs will require different procedures for generating randomisation schedules.

A practical method of randomisation is as follows: when an animal is enrolled for the study, it will be given a sequential number. Then, consulting the confidential randomisation list prepared previously by the sponsor, this number will refer to a figure or a code, which corresponds to an individual treatment.

In multicentre studies the randomisation procedures should be generated centrally. There may be advantages in having stratification or allocating several whole blocks to each centre. In a properly randomised multicentre study, the next animal to be randomise into a study should always receive the treatment corresponding to the next free number in the appropriate randomisation schedule or in the respective stratum as appropriate.

Details of the randomisation, which facilitate predictability, such as block length, should not be included in the protocol. The randomisation schedule should be filed securely by the sponsor or an independent party to ensure blindness is maintained.

In non-blinded randomised studies, the compliance of the investigator with the randomisation procedure can be checked by the monitor throughout the monitoring visits and afterwards in comparing the groups at inclusion. Discrepancies between groups will raise doubts about whether randomisation criteria have been correctly applied.

4 – BLINDED STUDY

When the assessment criteria are partly subjective, it is important that the investigator, the animal owner and other personnel involved in the animal observations do not know the treatment given. Blind conditions are less necessary when criteria are objective (mortality rate, mean daily weight gain, bacteriological parameters in sub-clinical mastitis).

There will always be a temptation to identify the products in a study; it is human nature. Therefore, it is not an easy task to implement a blinding procedure; a similar form and colour must be given to the two products (e.g. tablets incorporated in gelatine capsules), each individual treatment

must be encoded, etc. The code may be saved in a sealed envelope, to be opened only in case of an emergency or after the study has been completed.

Blinding may be achieved by the evaluating veterinarian being uninvolved in the treatment, thus remaining unaware of the treatment identity.

Blind experiments ensure that on average the groups, initially equal through randomisation, continue to be treated with equality

5 – STUDY DESIGN CONSIDERATIONS

5.1. Parallel Group Design – The most common clinical study design for confirmatory studies is the parallel group design in which study animals are randomised to one of two or more arms, each arm being allocated a different treatment. The treatments will include the investigational product at one or more doses, and generally one or more control treatments, such as placebo and/or active comparator.

5.2. Crossover design – In the crossover design, each study animal is randomised to a sequence of two or more treatments, and hence acts as its own control for the treatment comparisons. This simple manoeuvre is attractive primarily because it reduces the number of animals and usually the number of assessments required to achieve a specific power, sometimes to a marked extent. In the simplest 2x2 crossover design each animal receives each of two treatments in randomised order in two successive treatment periods, often separated by a washout period.

5.3. Factorial Design – In a factorial design two or more treatments are evaluated simultaneously in the same set of animals through the use of varying combinations of treatments. The simplest example is the 2x2 factorial design in which study animals are randomly allocated to one of the four possible combinations of two treatments, A and B say. These are: A alone; B alone; both A and B; neither A nor B. In many cases this design is used for the specific purpose of examining the interaction of A and B.

Contents of the protocol

The protocol is a written document, which states the rationale and objective of the study, and defines the conditions under which it is to be performed and managed. A well-designed study relies predominantly on a thoroughly considered, well-structured and comprehensive protocol, which must be established before the start of the study and signed by both the investigator and the representative of the sponsor. By signing the protocol, both parties agree that this is the exact way the study will be performed and that the study will be conducted according to the principles of GCP and applicable regulatory requirements.

The gestation of the protocol may take several months and results from the know-how of the company and other advisors. Therefore, it must be considered by the investigator as a **highly confidential** document.

As mentioned in the VICH GL9 (GCP) document the following items must be considered when a study is contemplated. The list is neither exhaustive nor is every item included applicable to all study protocols but is intended to give guidance.

1 – GENERAL INFORMATION

The protocol must have a title and a unique identifier, including date and version clearly located on the title page. The protocol must comprise administrative information on the investigator, representatives of the sponsor and all other participants in the study, e.g. names, addresses, qualifications, professional backgrounds.

2 – JUSTIFICATION AND OBJECTIVE

The objective and the justification of the study must be clearly stated. Ideally, the study should be designed to solve a single question. When this is not possible, a main objective and a secondary objective may be described. Common objectives are efficacy, drug interactions, palatability, ease of use, compatibility with husbandry procedures etc. All information should be described where relevant to the understanding of the objective of the study (pre-clinical or clinical data published or otherwise available) that justifies the conduct of the clinical study.

3 – SCHEDULE OF EVENTS

Schedule of key events occurring during the animal phase of the study should include: the expected date and time of commencement of the animal phase, the period during which the investigational and control veterinary product(s) are being administered, the post administration observation period, the withholding period (when applicable) and the termination date where known.

4 – STUDY DESIGN

Methodological characteristics of the study shall be detailed in the protocol. In particular, the blinding technique, the randomisation method and other bias reducing factors to be implemented must be clearly described. (see section Design of the Study)

5 – ANIMAL SELECTION AND MANAGEMENT

The protocol should specify:

- The source, number, identity and type of study animal to be used, such as species, age, gender, breed category, weight, physiological status and prognostic factors.

- The containment of the study animals e.g. pens, kennels and pastures; space allocation per animal; thermoregulation and ventilation of the accommodation.

- Permissible and non-permissible concomitant veterinary care and therapy, and procedures to ensure that animals will be handled in accordance with welfare requirements.

- The management of feed (including pasture management and the preparation and storage of mixed feeds) and water (including supply, availability and quality) and their presentation to the study animals. Documentation should be sufficient to establish that the nutritional requirements of the animals are met so as not to compromise the objectives of the study and to ensure that animal welfare requirements are met.

- Where nutritional status can be critical to the measurements to be collected in the study, describe any appropriate aspects such as feed composition and procedures for feed sampling and analysis.

6 – INCLUSION/EXCLUSION CRITERIA

In the protocol, inclusion, pre-admission exclusion and post-admission withdrawal/removal criteria are detailed. These absolute criteria must be kept in mind and strictly respected by the investigator.

7 – TREATMENTS

- Clearly and precisely identify the investigational veterinary product to permit an unambiguous determination of the specific formulation. Instructions for the further mixing (if any), packing and storage of the products should be stated.

- Identify control products by generic or trade name; dosage form, formulation (ingredients), concentration, batch number, expiry date. Storage conditions (e.g. at low temperature or protected from light) should be stated; investigational products should be stored and used according to label directions.

- If the veterinary product is administered in feed or water, describe the procedures for determining the concentration of the investigational veterinary product in the feed or water, including the sampling methods and assay methodologies (e.g. laboratory used, analytical method, number of replicates, assay limits, permitted analytical variation) to be used.

- Describe the dosing regimen (route, site of injection, dose, frequency and duration of administration) to be followed in administering the products.

- Describe the methods and precautions to be taken to ensure the safety of study personnel handling the products prior to and during administration.

8 – DISPOSAL OF STUDY ANIMALS, THEIR PRODUCTS AND INVESTIGATIONAL VETERINARY PRODUCTS

The protocol should describe the proposed disposal of the study animals and the care to be given to animals removed from the study in accordance with pre-established criteria.

The conditions for use of edible products from food-producing animals that must be followed in order to comply with the authorisation granted by the relevant regulatory authority should be stated (e.g. withdrawal period).

Procedures for the disposal and/or destruction of the investigational and control veterinary product(s) must be described.

9 – ASSESSMENT OF EFFICACY

- Define the effects to be achieved and the clinical end-point(s) to be reached before efficacy can be claimed; describe how such effects and end-points are to be measured and recorded, including the timing and frequency of study observations.

- Describe the special analyses and/or tests to be performed including the time of sampling and the interval between sampling, storage of samples and the analysis or testing.

- Select and define any scoring system and measurements that are necessary to measure objectively the targeted responses(s) of the study animal and evaluate the clinical response.

- Define the methods for computing and calculating the effect of the investigational veterinary product.

10 – ADVERSE EVENTS

Describe procedures for:

- Observing study animals with sufficient frequency to detect Adverse Events (AEs).
- Taking appropriate actions in response to observed AEs, such as locating and breaking blinding codes so that appropriate medical treatment can be given.
- Recording the AEs in the study documentation.
- Reporting AEs to the sponsor promptly.

11 – HANDLING OF RECORDS

Procedures should be specified for recording, processing, handling and retaining raw data and other study documentation required by the relevant regulatory authority. (See VICH GL9 Section 8.3 "Recording and handling study documentation".)

12 – STATISTICS

The statistical methods to be used to evaluate the effectiveness of the investigational veterinary product should be thoroughly described, including the hypotheses to be tested, the parameters to be estimated, the assumptions to be made and the level of significance, the experimental unit and the statistical model to be used. The planned sample size should be justified in terms of the target animal population, the power of the study and pertinent clinical considerations.

The handling of missing data and outliers should be described as part of the statistical section of the protocol or in an SOP. (See section 7.4 of EMA/CVMP Guideline on statistical principles for clinical trials for veterinary medicinal products)

13 – SUPPLEMENTS TO BE APPENDED TO THE PROTOCOL

- List any study-specific SOPs that apply to the conduct, monitoring and reporting of the study.
- Attach a copy of all data capture and event record forms to be used during the study.
- Include any other relevant supplements e.g. information to be provided to the owners of animals, instructions to study personnel.
- Instructions for preparation of protocol amendments (changes to the study protocol) and reporting of protocol deviations should be provided.

14 – REFERENCES

Citations to relevant literature referenced in the study protocol must be provided.

Part II: Investigator and Clinical Studies

Relationships between participants of a study

In order to successfully complete a clinical study, the investigator must interact with a number of other participants, e.g. the sponsor, the monitor, the animal owner and the clinical laboratory.

The main relationships between the various participants are summarised in the figure, and will be described in the following sections.

1 – RELATIONSHIPS BETWEEN INVESTIGATOR AND SPONSOR/MONITOR

Initiation of the Study

Prior to commencement of a study, the sponsor must, according to local regulations, submit an application for a field study authorisation or notify the relevant authorities.

There are further sponsor responsibilities that apply at initiation of multicentre studies or when work is delegated to a Contract Research Organisation (CRO). See boxes below.

USE OF MULTICENTRE STUDIES

The Sponsor should ensure:

- All investigators conduct the study in compliance with the study protocol.
- The data capture system is suitable for all study sites.
- All investigators are given uniform operating instructions.
- Communication between investigators is facilitated.

DELEGATION TO A CONTRACT RESEARCH ORGANISATION (CRO)

- If duties are delegated to a CRO the sponsor retains overall responsibility for the study.
- Any delegated duties should be confirmed in writing.
- All references to the sponsor duties also apply to the CRO.

The sponsor may then appoint the monitor(s) who will be in charge of the monitoring of the study. The sponsor and the monitor(s) will then choose the investigators who will be involved in the study.

The initial contact between monitor and investigator is generally informal (but confidential) and, most usually, done by a phone call. The objective of this first contact is to assess the investigator's interest in the study. If he/she declares an interest, an appointment for the initial visit is set up.

During the initial visit, the monitor ensures that the site is adequate for the study, and, if the site meets requirements, he/she provides the investigator with all the information on the study including the experimental protocol.

In particular, the investigator shall be informed of the pre-clinical data (in vitro studies, pharmacokinetic studies, dose-titration studies, safety studies) which justify the dose that will be used in the target species.

The investigator must keep all this information highly confidential.

ADEQUACY OF THE SITE

Key points to be checked by the monitor at the initial visit:

- Availability of the investigator and his staff: they must have the time to devote to the study, and there should be no conflict of interest with studies conducted for other sponsors.
- Case recruitment: the investigator should be able to include the required number of cases within the scheduled enrolment period.
- Technical equipment: when the protocol requires particular technical equipment (X-ray, ECG, etc...), the equipment must be inspected by the monitor to ensure it meets the requirements of the protocol.
- Qualification of the investigator: the monitor must ensure that the investigator is properly qualified and possesses the required expertise. This is usually done by means of a CV.
- Ability to store investigational and control products and samples.

During this initial meeting, the investigator should ask the monitor for clarification of any point he does not fully understand. Conversely, the monitor should make sure that the entire protocol is understood by the investigator, and must explain any ambiguous or questionable aspect, which, if necessary, can be the subject of an amendment to the protocol. At the end of the meeting, investigator and monitor must reach a consensus on the protocol contents.

Then the monitor can leave all the material necessary for the study (products, protocols, clinical reports forms, etc.).

Finally, the monitor must prepare a report of this initial visit to be archived in the Study File.

GENERAL RESPONSIBILITIES OF THE MONITOR

- To link the sponsor and the investigator
- To be trained in QC techniques
- Not to bias the data collection or study outcome
- Ensure that informed consent is obtained from the owners
- To visit and contact the investigator before, during and after the study
- To check the suitability of site, space, facilities, equipment, staff and potential animal numbers
- To ensure that all staff are fully informed of requirements and responsibilities
- Confirm traceability of investigational and control veterinary products
- Maintain accurate and complete records of all contacts
- To ensure that the study is being run according to the protocol and all data are correctly and completely recorded
- Ensure that illegible, missing or corrected documents are explained
- To report any adverse event to the sponsor

Where applicable, a similar visit will be made by the monitor to any clinical or analytical support laboratory involved in tests and investigations during the study.

The assurance of quality of every aspect of the study is a fundamental component of sound scientific practices. The principles of GCP support the use of Quality Assurance (QA) for clinical studies. All participants in clinical studies are encouraged to adopt and adhere to generally recognized sound QA practices.

It is envisaged that QA can provide an independent auditing service leading to quality improvement measures.

Monitoring the Study

The monitor of the study will keep in touch with the investigator during the course of the study. Moreover, he/she will pay regular visits, or intermediate visits, to the investigation site. The frequency of the visits have been discussed and agreed during the initial visit. It depends on the protocol requirements (volume of data collected, level of recruitment...). The objectives of such a visit are:

- to review the current situation of the study in progress: how many cases have been recruited? Has there been any difficulty in complying with the protocol? Has any incident been observed during the course of the study, in particular any death or an adverse event, which was not reported? Has there been any change in the investigator's staff?

- to check that the course of the study in the investigator's site complies with the protocol (in particular with selection criteria, dates of assessment visit or test, drug delivery etc.).

- to examine the Individual and/or Collective Record Sheets: the monitor will make sure that the quality of the information collected in the record sheets is correct. All data requested should be recorded. Erroneous, aberrant or contradictory information should be detected and, if possible, corrected by the investigator on site according to the agreed correction procedure.

These intermediate visits require the availability of the investigator who must reserve enough time for each meeting and provide all data currently on file at the time of the visit.

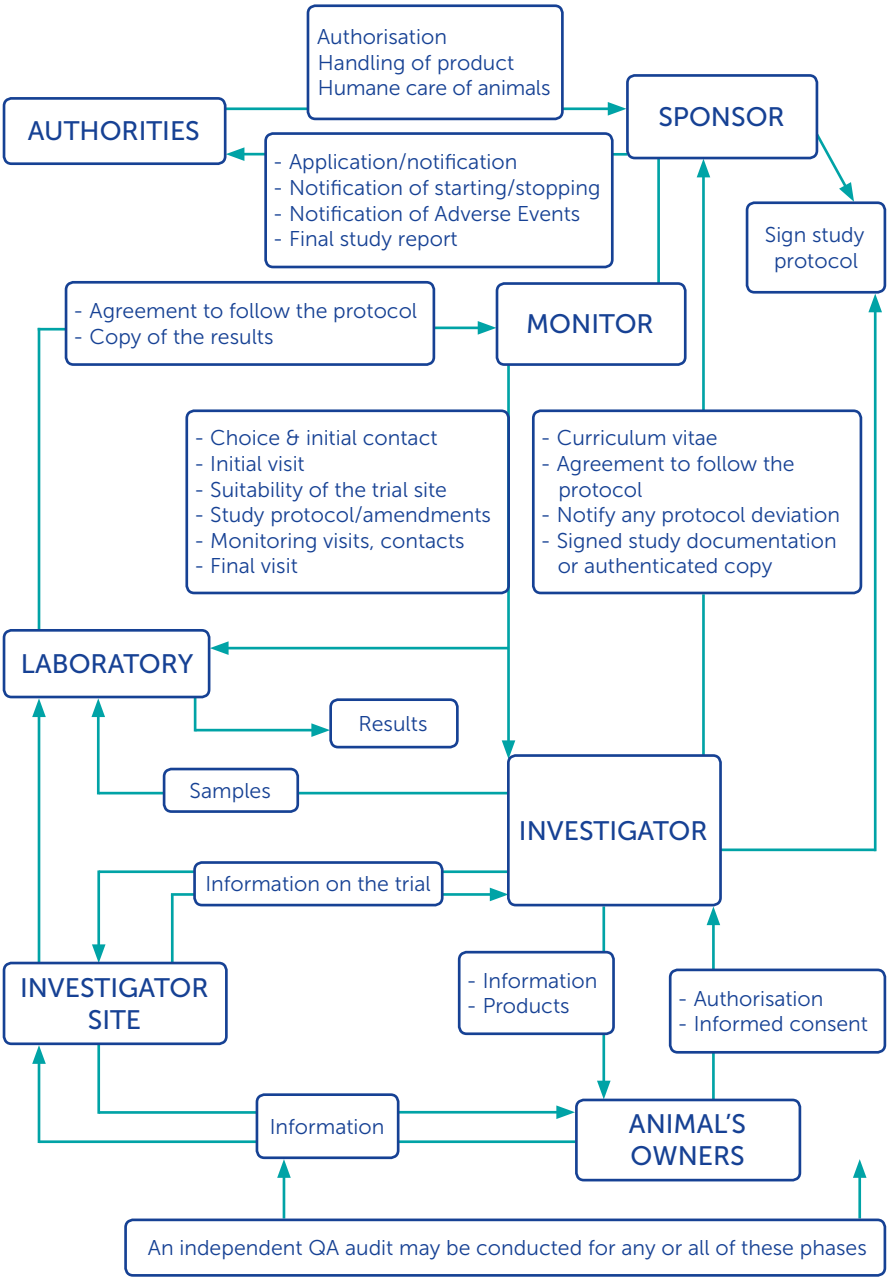
Between intermediate visits, contact between investigators and sponsor/monitor will be maintained by any convenient means of communication.

Visits and other contacts will be recorded by the monitor and forwarded to the sponsor to be archived in the study file (paper trail concept). Contact records should also be documented independently by the investigator. Remember that these may be subject for examination and comparison at audit and inspection.

Final Visit

At the end of the study, the monitor will pay a final visit: in addition to the aforementioned actions, he/she will collect all the data and assure the accountability of drug supplies.

Relationships between participants of a study



2 – RELATIONSHIPS BETWEEN INVESTIGATOR AND ANIMAL OWNER

The success or miscarriage of a clinical study often depends on the animal owner's motivation and compliance with the protocol requirements. Therefore, the enrolment visit is much more than a simple routine consultation, and will require extra time, diplomacy and persuasion from the investigator to inform and motivate owners of animals.

The investigator must provide the owner of any animal he would like to include in a study with written information on the study.

He must give a clear presentation of the disease to be treated or prevented by the test product, of the risks and benefits for the animal, of the disadvantages or constraints resulting from participation in the study.

In the case of pets the investigator must take into account emotional aspects and explain to the owner the significance of a clinical study. In many cases the pet owner may be concerned that the animal is being subjected to an experimental procedure.

In food-producing study animals, economic aspects must be taken into account, with for example the economic losses which could result from a long withdrawal period. Furthermore, the investigator must obtain the written consent of the owners of food-producing animals. The keeper of the animals must be given a letter stating the withdrawal period, and a letter for counter signature which the investigator or sponsor retains.

Then, all along the study, the investigator will have to ensure that the owner keeps being co-operative, does what was asked of him at the enrolment visit and still complies with the protocol.

3 – RELATIONSHIPS BETWEEN INVESTIGATOR AND HIS/HER STAFF

During the course of the study, the investigator's staff must be informed about the participation of his facility in a clinical study. All staff members must know which animals are participating to the study, to record any relevant information on the CRF and to pay special attention to what the animal owner is reporting.

Technicians may be involved in the study and be responsible for technical actions such as sampling or weighing of animals. In this case, the investigator will be the supervisor of these technicians.

4 – RELATIONSHIPS BETWEEN INVESTIGATOR AND CLINICAL LABORATORIES

If the protocol requires analysis of clinical samples, it may be necessary to involve the services of a clinical laboratory.

> Good Clinical Practice requires that the interactions between the various individuals involved in the study are recorded and all records archived.

Good investigational conduct

Although the overall responsibility for a clinical study remains with its sponsor, an important part of this responsibility is shared with each investigator.

By nature of his profession, a veterinarian has responsibilities towards the animal, its owner and the society. Veterinarians, who participate in a clinical study as clinical investigators, also have obligations to the sponsor of the study.

GENERAL RESPONSIBILITIES OF THE INVESTIGATOR

- To conduct the investigation according to the protocol, relevant SOPs, GCP and applicable regulatory requirements
- To protect the health, and welfare of the personnel and animals involved in the study, and the environment and consumer
- To control investigational and control veterinary products
- To obtain informed consent
- To control animals under investigation
- To report any adverse event to the sponsor
- To assure sufficient and adequate staff, facilities, time, equipment and veterinary supervision are available
- To ensure appropriate retention of study data/ documentation
- To permit monitoring, Quality Auditing and Inspection
- To maintain confidentiality

1 – COMPLIANCE WITH PROTOCOL

The protocol describes all matters related to the design, execution and evaluation of the study. It is therefore essential that every investigator carefully reads it and makes sure that he is able to perform the study as described. When certain aspects of the protocol are unclear, whether at the first reading or later during the study, the investigator, before taking any action, must contact the representative of the sponsor i.e. the monitor.

The design of the study has been carefully planned. If every investigator were to make his/her own changes, then the results would become completely useless. Deviations from the protocol should, therefore, be prevented as much as possible.

Nevertheless, in certain cases, it might not have been possible to follow the protocol. Then, all details of the deviations should be recorded on the appropriate forms and the monitor of the study be notified.

SIGNIFICANT DEVIATIONS IN A CLINICAL INVESTIGATION

- Submission of inaccurate data
- Failure to follow the protocol
- Failure to obtain informed consent
- Failure to maintain adequate record of drug accountability
- Failure to account for all animals included in the study

Where an investigator wishes to have recourse to systematic deviations from the protocol, he must first inform the monitor and wait for the written approval by the sponsor.

The best of protocols cannot withstand lack of rigour from investigators. Adherence to the protocol is essential for correct evaluation of the data.

2 – ANIMALS AND OWNERS

Animal selection

Animal selection is a critical point because the investigator must not only ensure that the "objective" inclusion criteria for enrolment in the study are met, but also select only the most co-operative owners. Indeed, for the study to run efficiently, it is not only essential to have the right animal, but also the right owners, whose co-operation is a key element: pets must be brought in for repeated examinations while farm animals must be weighed, have their feed intake recorded, etc. Not all owners can or will follow the instructions of the veterinarian.

Informed consent

Owners or their agent must give their "informed consent" to their animals' enrolment into the study. Therefore, the investigator must inform them of their rights and responsibilities, and make them aware of the risks and possible discomfort linked to the investigation.

For studies involving food-producing animals, owners shall be informed in writing of the requirements for disposal of their animal and for any obligatory withholding periods for meat, milk, eggs etc. A copy of this notification must be signed and dated by the owner and is part of the study documentation.

Withdrawal from the study

Withdrawal of animals from the study will introduce bias and should be avoided. Only when justified, for example for animal welfare reasons, this can be considered. Where animals have been withdrawn from a study, investigators must justify the reasons for the withdrawal on the individual record sheet forms and report these to the sponsor, via the monitor.

3 – RECORDING

The protocol gives clear instructions about what must be recorded, how it should be recorded, by whom and when. If the protocol is not clear, the monitor of the study must be contacted.

The original records, the so-called raw data, are the basic source of information. Therefore, they must be gathered with due accuracy and rigour. Raw data are the first-hand records of an observation and are collected in individual and/or collective record sheets. They can be hand-written or electronic and should be securely stored.

The methods of computerised record keeping and retention should maintain the same principles and degree of confidence as paper systems. Electronic signatures should identify the person responsible for the observation and allow for changes, which must be documented and traceable.

The proper recording of data is of critical importance and some basic rules must be followed (see below).

GOOD RECORDING OF DATA

- Use the appropriate sheets.
- Complete the sheets immediately after collecting the data.
- Fill in the sheets completely, record data to the accuracy measured and include units.
- Only use permanent medium, do not use a pencil for writing, ensure original entries are unalterable for electronic records.
- If there is a mistake:
  1. cross out the incorrect part, but so that it can still be read;
  2. put in the correct recording;
  3. sign and date the correction;
  4. clarify why any alterations were made.
- The person observing and recording the data must sign and date his/her recording.
- Write legibly.
- Describe briefly situations and conditions with scientifically accepted terminology.
- Explain why certain observations/measurements are missing.
- In case of computerised data not equipped with electronic date/signatures: make a printout of the data and sign/date it.
- Facsimile transmissions and transcribed data are not considered raw data.

In case copies or transcription of the raw data are required, an authenticated copy of that data should be made. This should include clarification why the copy or transcription was made, signed and dated by the person making the copy or transcription and the original, copy and clarification should be kept together in the study documentation.

4 – INVESTIGATIONAL AND CONTROL VETERINARY PRODUCT

Generally the product under investigation is not yet registered and can, therefore, only be used when the national authorities have issued a study licence. Such a licence may contain certain conditions for the distribution and administration of the product and give withholding periods for animal products. The sponsor and the investigator must comply with these conditions.

GOOD HANDLING OF INVESTIGATIONAL AND CONTROL VETERINARY PRODUCT

- Comply with protocol.
- Respect dispensing and storage instructions.
- Do not transfer the product to alternative packaging.
- Complete dispensing logs.
- Maintain an accountability of the stocks.
- Return all unused supplied products to the sponsor at the end of the study.

In addition, accurate records of the investigational and control veterinary product(s) must be kept by the investigator: what has been received, used (and for which animals) and returned. The objective of these measures is to prevent any test product being used outside the study, and to prevent residues of the test product appearing in food for human consumption.

At the end of the study, any unused product must be returned to the sponsor, via the monitor, or destroyed as instructed.

5 – SAMPLES

The investigator should ensure that all samples that are collected during the course of the study are appropriately identified to preclude loss of the identification of the samples and that they are handled and stored appropriately.

The protocol provides detailed instructions, i.e. standard operating procedures (SOPs), on how to take and handle samples.

GOOD HANDLING OF SAMPLES

- Ensure that samples are packed, stored in well-labelled and suitable containers.
- Identify the SAMPLES properly.
- Do not use ink for samples that will be frozen (when defrosted the text will become illegible due to the condensation).
- Attention should be given to check opening hours of the laboratory when dispatching samples.

6 – ADVERSE EVENTS (AE)

Any adverse event should be reported immediately to the representative of the sponsor and recorded on the appropriate forms.

It is not the role of the investigator to decide whether an adverse event is worth reporting. The investigator must report all such events and the sponsor/monitor, who has contact with all study sites, will decide if and what further action is required.

Depending on the nature and the frequency of the reactions, it may be decided to break the blinding code, to stop or even cancel the study. But this decision cannot be made by the investigator on his own. Moreover, no code can be broken without the consent of the sponsor or the monitor, except in a situation where animal welfare may be compromised.

> When an adverse event occurs, even in doubt, REPORT IT

Any unanticipated events that may affect the quality and integrity of the study and the corrective action taken in response should be documented by the investigator and described in the report, e.g. snow storm.

7 – CONFIDENTIALITY

The development of a new veterinary medicinal product is a costly and time-consuming activity and the data collected during the study maybe of great commercial value.

Maintaining the secrecy of confidential information received from the sponsor in connection with the medicinal product and with the planning, execution or evaluation of the study is one of the responsibilities of the investigator.

Also the privacy and personal identify of animal ownership should be kept confidential. If data verification procedures demand inspection of such details, these may only be accessed by designated personnel.

INVESTIGATOR GOLD STANDARD

- Confidentiality
- Discipline
- Precision

8 – DATA AND THE FINAL REPORT

8.1 – Data and Data Integrity – the credibility of the numerical results of the analysis depends on the quality and validity of the methods and software used both for data management (data entry, storage, verification, correction and retrieval) and also for processing the data statistically. Data management activities should therefore be documented; it may be helpful to describe basic data management procedures in specific SOPs. The computer software(s) used for data management and statistical analysis should be reliable and documentation of appropriate software testing procedures should be available.

8.2 – Raw Data – these are original worksheets, calibration data, records, memoranda, and notes of firsthand observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, magnetic, electronic and optical media, information recorded from automated instruments, and hand recorded data sheets.

Care should be taken over e-mails where critical decisions are made by these media. Here a print out must be taken for the file and should be signed by the appropriate persons.

8.3 – Study Documentation – these are as detailed above and should permit the reconstruction of the study in totality. All documentation should be stored for the period of time required by the relevant regulatory authority. Study documentation includes but is not limited to: Study protocol, raw data, (see VICH GL GCP Section 8.2.2), Safety Reports, Final Study Reports and other Reports.

Recording and handling study documentation should be carried out in an organised way that prevents loss, damage or unauthorised correction. Units where used should be clearly stated and where there is the need to copy documents this should be performed in a controlled way with appropriate authentication. Correction to data must be made in a way as to not obscure the original entry, signed and dated with an explanation. Computerised record keeping should follow the above criteria.

8.4 – Data retention. During and post study – all study documents should be stored in a manner that protects them from deterioration, destruction, tampering and vandalism, in accordance with the type of records. Orderly storage and easy access are key criteria. The location of the data should be stated in the Final Study Report.

8.5 – The Final Study Report (FSR) – this is a comprehensive description of a study of an investigational veterinary product that is written after the collection of all the raw data is complete or the study is discontinued. It is a complete description of the objectives, methods and experimental materials (including statistical analyses), presents the study results and contains a critical evaluation of the study results.

It is the responsibility of the sponsor to provide a FSR for any study in which an animal has been treated with an investigational veterinary product, whether the study has been completed as planned.

The author of the FSR may be:

- The sponsor
- The investigator
- Both parties

If the investigator does not participate, all relevant data must be supplied to the sponsor and a statement provided by the investigator that the report is a true and accurate reflection of the data and the study that they conducted. Signatories to reports also take on legal responsibilities.

The content of the FSR should be compiled in accordance with the section 7.3 of the VICH GCP Guidelines. In actuality the content is almost a mirror image of the Protocol described earlier in this text, written as "what was performed, when and by whom".

8.6 – Statistics and the FSR – in the statistical section of the FSR, the statistical methodology should be clearly described. It should also describe when methodology decisions were made in the clinical study process.

Primary data should normally be provided as part of the reporting process and sufficient information, summary tables, and reports on analyses be included in the statistical output of the report so that the reviewer can easily review the FSR from the raw data to the final inferential claims. In particular, a reviewer should be able to check a statistical procedure by taking the raw data, applying the statistical method and software to arrive at the same conclusions presented in the report.

The effect of all losses of experimental units or data, withdrawals from treatment and major protocol deviations on the main analyses of the primary variable(s), should be considered. Experimental units lost to follow-up, withdrawn from treatment, or with a severe protocol deviation should be identified, and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

Descriptive statistics form an indispensable part of reports. Suitable tables and/or graphical presentations should illustrate clearly the important features of the primary and secondary variables. The results of the main analyses relating to the objectives of the study should be the subject of a descriptive presentation.

9 – INSPECTION AND AUDIT

Audit

Quality assurance is the systematic and independent examination of study related activities and documents to determine whether the study being evaluated is or was properly conducted and whether the data are or were recorded, analysed and accurately reported according to the study protocol, study related SOPs, GCP and the applicable regulatory requirements.

There should be an assurance that the quality and integrity of data from a clinical study is maintained by implementing a quality audit procedure that is consistent with well-recognized principles of quality assurance.

Official inspection

In some countries, the regulatory authorities may have the legal duty to check if clinical studies are being carried out in accordance with the conditions laid out in the study licence. Then, not only the sponsor, but also the investigator and animals owners may be inspected.

GOOD CLINICAL PRACTICE FOR VETERINARY MEDICINAL PRODUCTS THE KEY FACTORS

- SOPs
- Qualified, trained and experienced personnel
- Protocol review
- Careful selection of study animals
- Acquisition of informed consent
- Completion of procedures according to protocol
- Accurate and clear case record forms
- Exact accountability of investigational and control veterinary products
- Compliance with protocol
- Reporting of adverse events
- Ongoing quality control checks by all persons at each step of the procedure
- An accurate report describing fully the clinical study
- Suitably archived Data and Documentation to allow reconstruction of the study
- Confidentiality

Glossary

Adverse Event (AE)
Any observation in animals that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, whether or not considered to be product related.

Applicable Regulatory Requirement(s)
Any law(s) and regulation(s) of the relevant regulatory authority addressing the conduct of studies using investigational veterinary products.

Audit
A systematic and independent examination of study related activities and documentation to determine whether the study being evaluated is or was properly conducted and whether the data are or were recorded, analyzed and accurately reported according to the study protocol, study related standard operating procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

Authenticated Copy
A copy, which is a complete reflection of an original document, that bears or contains a statement, signed and dated by the individual(s) making the copy, certifying that such copy is complete and accurate.

Blinding (Masking)
A procedure to reduce potential study bias in which designated study personnel are kept uninformed of the treatment assignment(s).

Case Report Forms/Data Capture Forms/Record Sheets
Printed, optical, electronic, or magnetic documents specifically designed to record study protocol-required and other observations of study animals or laboratory results.

Clinical Study
A single scientific experiment conducted in a target species to test at least one hypothesis relevant to the proposed effectiveness claim(s) or to in-use safety in the target animal for a veterinary product under investigation. For the purpose of this guidance, the term clinical study and study are synonymous.

Compliance (in relation to studies)
Adherence to the study protocol, relevant SOPs, Good Clinical Practice, and the applicable regulatory requirements.

Control Product
Any approved product used according to label directions, or any placebo, used as a reference in a clinical study for comparison with the investigational veterinary product under evaluation.

Contract Research Organisation (CRO)
An individual or organization contracted by the sponsor or investigator to perform one or more of the obligations of the sponsor or investigator.

Disposal of Investigational Veterinary Products
The fate of investigational veterinary and control products during or following completion of the study. For example, after complying with any restrictions to minimize public health concerns, the products may be returned to the sponsor, incinerated or disposed of by other approved methods.

Disposal of Study Animals
The fate of the study animals or their edible products during or following completion of the study. For example, after complying with any restrictions to minimize public health concerns, animals may be slaughtered, returned to the herd, sold or returned to their owner.

Final Study Report (FSR)
A comprehensive description of a study of an investigational veterinary product that is written after the collection of all raw data is complete or the study is discontinued and that completely describes the objectives and experimental materials and methods (including statistical analyses), presents the study results and contains a critical evaluation of the study results.

Good Clinical Practice (GCP)
A standard for the design, conduct, monitoring, recording, auditing, analysis, and reporting of clinical studies. Adherence to the standard provides assurance that the data and reported results are complete, correct and accurate, that the welfare of the study animals and the safety of the study personnel involved in the study are ensured, and that the environment and the human and animal food chains are protected.

Informed Consent
A documented process by which an owner, or owner's agent, voluntarily confirms the owner's willingness to allow their animal(s) to participate in a particular study, after having been informed of all aspects of the study that are relevant to the decision to participate.

Inspection
The act by a relevant regulatory authority of conducting, in accordance with its legal authority, an official review of study documentation, facilities, equipment, finished and unfinished materials (and associated documentation), labelling, and any other resources related to the registration of an investigational veterinary product and that may be located at any site related to the study.

Investigational Veterinary Product
Any biological or pharmaceutical form of, or any animal feed containing one or more active substances being evaluated in a clinical study, to investigate any protective, therapeutic, diagnostic, or physiological effect when administered or applied to an animal.

Investigator
An individual responsible for all aspects of the conduct of a study at a study site. If a study is conducted by a group of individuals at a study site, the investigator is the leader of the group.

Monitor
An individual responsible for overseeing a clinical study and ensuring that it is conducted, recorded, and reported in accordance with the study protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.

Multicenter Study
A study conducted according to a single study protocol at more than one site.

Quality Assurance (QA)
A planned and systematic process established to ensure that a study is performed and the data are collected, documented (recorded) and reported in compliance with this guidance and the applicable regulatory requirements.

Quality Control (QC)
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the study-related activities have been fulfilled.

Randomization
The process of assigning study animals (or groups of study animals) to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Raw Data
Any original worksheets, calibration data, records, memoranda and notes of firsthand observations and activities of a study that are necessary for the reconstruction and evaluation of the study. Raw data may include, but are not limited to, photographic materials, magnetic, electronic or optical media, information recorded from automated instruments, and hand recorded datasheets. Facsimile transmissions and transcribed data are not considered raw data.

Regulatory Authorities
Bodies having the statutory power to regulate. In this guidance, the expression 'regulatory authorities' includes the authorities that review submitted clinical data and conduct inspections.

Sponsor
An individual, company, institution or organization which takes responsibility for the initiation, management, and financing of a clinical study for the veterinary product under investigation.

Standard Operating Procedure (SOP)
A detailed, written instruction to facilitate consistency in the performance of a specific function.

Study Animal
Any animal that participates in a clinical study, either as a recipient of the investigational veterinary product or as a control.

Study Protocol
A document signed and dated by the investigator and the sponsor that fully describes the objective(s), design, methodology, statistical considerations and organization of a study. The study protocol may also give the background and rationale for the study but these could be provided in other study protocol-referenced documents. Throughout this guidance the term study protocol includes all study protocol amendments.

Study Protocol Amendment
A written change or modification of the study protocol effected prior to the implementation of the protocol or execution of the changed or modified task. Study protocol amendments should be signed and dated by the investigator and sponsor and incorporated into the study protocol.

Study Protocol Deviation
A departure from the procedures stated in the study protocol. Study protocol deviations should be recorded as a statement signed and dated by the investigator describing the deviation and the reason for its occurrence (if identifiable).

Target Animal
The specific animal by species, class and breed identified as the animal for which the investigational veterinary product is intended for use.

Veterinary Product
Any product with approved claims to having a protective, therapeutic or diagnostic effect or to affect physiological functions when administered to or applied to an animal. The term applies to therapeutics, biologicals, diagnostics and modifiers of physiological function.

Health for Animals
global animal medicines association

168 Avenue de Tervueren, Box 8
1150 Brussels, Belgium

info@healthforanimals.org
www.healthforanimals.org

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