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Informed Consent Forms for Studies that Enroll Client-Owned Companion Animals

Guidance for Industry

Draft Guidance

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For further information regarding this document, contact Steven Fleischer, Center for Veterinary Medicine (HFV-110), Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, 240-402-0809, email: steven.fleischer@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

U.S. Department of Health and Human Services
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Center for Veterinary Medicine (CVM)
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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

The FDA's Center for Veterinary Medicine (CVM) is issuing this guidance to provide recommendations on informed consent forms (ICF) used for studies that enroll client-owned companion animals (dogs, cats, and horses). CVM recommends all studies conducted with client-owned companion animals use an ICF and be conducted in accordance with Good Clinical Practice (GCP) guidelines.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

As defined in Guidance for Industry (GFI) #85 (VICH[1] GL9), "Good Clinical Practice"[2] and for the purposes of this guidance, informed consent is 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 may be relevant to the owner's decision to participate. The sponsor or investigator should ensure the owner is provided with adequate information and time to allow for an informed decision about voluntary participation in a clinical investigation. CVM recommends an investigator, whenever possible, provide an owner with a copy of the ICF at least 12-24 hours prior to enrollment in the study (for example, at the time of screening) to allow sufficient time for the owner to review the information, formulate any questions, and consider whether to participate.

[1] International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products

[2] https://www.fda.gov/media/70333/download

CVM recommends animal drug sponsors consider the components of the ICF as described in this ICF guidance early during the development of their drug. Discussions regarding the ICF may be particularly important for novel drug classes, novel dosage forms of new animal drugs, or previously unapproved uses or new conditions of use of an approved animal drug (for example, novel routes of administration or target animal species). Additional discussions may be warranted as new information pertaining to safety or effectiveness becomes available during product development. Sponsors are encouraged to contact CVM to discuss the ICF or any questions they may have about the ICF.

III. Scope

The purpose of this guidance is to provide recommendations on informed consent forms used in studies that enroll client-owned companion animals. This guidance is not applicable to studies conducted in food-producing animals. This guidance is directed at individuals who develop ICFs and conduct studies in client-owned companion animals.

The guidance provides recommendations regarding the following items:

- The use of plain language.
- The avoidance of coercive, unduly influential, or exculpatory language.
- The basic elements of an ICF, including:
    - A description of the clinical investigation.
    - A description of benefits and compensation.
    - Statements regarding participation, termination, and withdrawal.
    - A description of procedures, treatments, and potential discomforts.
    - A description of risks associated with participation in the study.
    - Providing significant new findings to owners.
    - Statements on confidentiality.
    - Signature(s).
    - Contacts.
- Informed consent form discussion with CVM.

IV. Terminology

Investigator: The investigator is an individual, qualified by training and experience, responsible for all aspects of the conduct of the study. These responsibilities may include: the dispensing and administration of the investigational and control veterinary product(s), the implementation of the study protocol, the collection and reporting of the study data, and the protection of the health and welfare of the personnel involved in the study and the animals during the study.

Study animal: An animal participating in a clinical study.

V. General Considerations

A. Use of plain language

The U.S. Department of Health and Human Services (HHS) defines health literacy[3] as follows:

- **Personal health literacy**: the degree to which individuals have the ability to find, understand, and use information and services to inform health-related decisions and actions for themselves and others.
- **Organizational health literacy**: the degree to which organizations equitably enable individuals to find, understand, and use information and services to inform health-related decisions and actions for themselves and others.

Health literacy incorporates a range of abilities: reading, comprehension, and analyzing information; decoding instructions, symbols, charts, diagrams; weighing risks and benefits; and, ultimately, making decisions and taking actions. Everyone, no matter how educated, is at risk for misunderstanding health information if the topic is emotionally charged or complex.[4] These general concepts are applicable to investigational new animal drug studies that enroll client-owned companion animals.

CVM recommends the ICFs use language understandable to owners (i.e., plain language) of potential study animals. The ICF should incorporate all the information into a single document to avoid the possibility that an owner does not receive all the relevant information. The ICF should be in the owner's primary language. If an owner is not fluent in English, a translated document, in plain language, is preferred over ad hoc translation.

Documents should avoid the use of technical, scientific, or medical terminology. When such terms are necessary or unavoidable, the document should explain them in context and/or provide a definition using plain language. All complex concepts, including risks and benefits, should be explained in plain language. The owner should have the opportunity to ask questions and have those questions answered.

The Agency for Healthcare Research and Quality[5] makes some the following recommendations regarding ICFs for human subjects enrolled in research studies and they are generally applicable to the owner or agent of client-owned companion animals enrolled in investigational new animal drug studies:

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[3] https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/clear-communication/health-literacy

[4] https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/clear-communication/health-literacy

[5] https://www.ahrq.gov/sites/default/files/publications2/files/ictoolkit.pdf

- Keep the reading grade level low. It is recommended, where possible, for documents to be written at the 5th or 6th grade level.[6]
- Do not use medical jargon.
- Use the active voice.
- Use short sentences with simple sentence structure.
- Use easily legible fonts and font size.
- Do not use all capital letters or italics.
- Use wide margins and avoid fully justified alignment of text. For example, a line length of 50 characters and spaces or fewer may be easier to read.
- Break up text into manageable sections using headings and subheadings.
- Documents that use large fonts, short lines, white space, bulleted lists, and headings to break the text into manageable pieces are easier to read than short, dense documents.

Charts, tables, or graphics that outline what happens at each visit may simplify the ICF and assist owners in understanding what participation in the clinical investigation may entail.

Although there are no Federal laws that regulate the informed consent process for investigational new animal drug studies that enroll client-owned companion animals, for similar information on informed consent for studies that enroll human subjects, review 21 CFR 50.20, as well as FDA guidances, "Informed Consent: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors,"[7] and "A Guide to Informed Consent."[8] These documents describe the law surrounding informed consent for human subjects and the FDA's interpretation of these laws.

B. Coercion and undue influence

Coercion and undue influence are the use of pressure, either by promises of benefits or threats of harm, whether explicit or implied, to persuade the owner or agent of a potential study animal to participate in the study. All efforts should be made to eliminate or minimize the possibility for undue influence or coercion, intentional or inadvertent, to play a role in the owner's decision. It is important to compose the ICF to avoid the possibility that the owner will feel coerced or unduly influenced, whether or not actually intended, because a valid consent depends on the owner's ability to freely decide on their own whether or not to allow their animal to participate in the

[6] https://www.ahrq.gov/health-literacy/improve/precautions/tool11.html

[7] https://www.fda.gov/media/88915/download

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guide-informed-consent

study. The ICF should provide factual, relevant information and avoid persuasive language.

The ICF should avoid statements that:

- Could be false or misleading;
- May cause owners to believe the investigation has the FDA's endorsement; or
- Could give rise to overly optimistic expectations as to risks, prognosis, outcome, safety, effectiveness, or any matter that might influence the owner to participate.

To help ensure the integrity of the study, CVM recommends avoiding the enrollment of animals owned by investigators, employees or relatives of investigators or the sponsor, or any person with any direct or indirect interest in the outcome of the study. For example, an employee of an entity with an interest in a study may be vulnerable to influence or coercion. Consider including a statement for signature that the owner does not have a direct or indirect interest in the study.

The ICF should make clear that clients may remove their animals from the study at any time without penalty or loss of benefits to which the client is entitled. The ICF should not pressure the owner to continue participation in the study by suggesting, implicitly or explicitly, that leaving the study would cause harm to the animal. The ICF should be consistent with any oral information given to the owner.

C. Exculpatory language

The ICF should not incorporate any language that waives or appears to waive any of the owner's legal rights or releases the investigator, sponsor, institution, or other entity or its agents from any legal liability it may have or come to have.

The ICF should not require the owner to affirm that they "understand" the information provided. The owner should also not be asked or required to affirm that the ICF provides all relevant information. Any language intended to limit the study investigator's responsibilities or duty of care is inappropriate. A signed statement by the client confirming receipt of the written information is more appropriate, as further discussed below.

VI. Basic Elements of an Informed Consent Form

A. Description of the clinical investigation

1. Identifying the clinical investigation as investigational. The ICF should contain a brief introductory paragraph that:

    a. States the product is investigational, and safety and effectiveness have not been demonstrated or evaluated for the indicated investigational use. If the

product has been approved for other uses under a new animal drug application (NADA), the ICF should include that information.

b. States the purpose of the study is for the investigational use of the veterinary product rather than to provide medical treatment to the study participants.

c. Describes the objective of the clinical investigation (for example, to evaluate the safety and effectiveness of the test article or to evaluate a different dose or route of administration of an approved drug).

If the ICF contains multiple pages or sections, repeating this information in other parts of the ICF may aid the owner in understanding the nature of the clinical investigation.

The ICF should not include statements that suggest the investigational veterinary product (IVP) is "safe" or "effective" under the proposed conditions of use. The ICF may incorporate factual information that accurately reflects data from completed studies.

2. Identify the treatment groups and number of study animals. The ICF should include the following:

   a. The approximate number of study animals intended to be enrolled in the study.

   b. A description of the treatment groups, including control groups (placebo, active control, or no treatment), presented in plain language.

   c. The likelihood of the animal being assigned to a control group versus a treatment group (for example, the animals have a 33% chance of being enrolled in the control group in a field study with a 2:1 treated:control enrollment ratio).

3. Alternative procedures or treatments:

   The ICF should include information about appropriate alternatives, if any, to entering the study that may be advantageous to the study animal. The ICF should identify:

   a. Procedures or treatments, if any, that animals with the condition(s) would likely receive if they choose not to participate in the study, including alternatives such as approved drugs (for example, an approved oncology drug) for the study animal's condition, or other forms of therapy (for example, surgery). This should include identifying any procedures and treatments that will not be performed or allowed during the study (for example, a requirement to not receive insulin during a study investigating a novel drug to treat diabetes mellitus). CVM recommends the ICF briefly describe these procedures or treatments, if any, first and then provide the

information about the study. This sequence allows the owner to understand how the study differs from the care their animal might otherwise receive.

b. Potential consequences of these differences in care, if known (for example, a worsening of the disease or clinical condition than would be expected with an approved drug).

4. Owner's responsibilities to comply with the protocol:

The ICF should state the owner's responsibilities while participating in the clinical investigation. Examples of responsibilities include, but are not limited to, the following:

a. To maintain masking, only discuss treatment information with pre-specified study personnel involved in the conduct of the investigational study. Depending on treatment, masking, and other study requirements and circumstances, do not disclose treatment information to investigators, staff, other owners, or others.

b. Complete an owner diary, questionnaire, or other means of recording events and data. Owners should be provided with the means to use sound documentation practices that are attributable, legible, contemporaneous, original, and accurate (ALCOA).

c. Comply with medical, dietary, or other restrictions for the animal during the study.

d. Know when to contact the Investigator regarding any clinical concerns (for example, whether to contact the Investigator regarding any vomiting, diarrhea, anorexia, or clinical concerns prior to the next scheduled visit).

e. Know when to return for study visits. If the study is complex or the duration is long, consider including a study schedule or calendar.

If a detailed description of every responsibility would make the ICF too lengthy, CVM recommends generally listing the responsibilities and describing additional details of all owner responsibilities in an addendum.

Charts, tables, or graphics that outline what happens at each visit may simplify the ICF and assist owners in understanding what participation in the clinical investigation will involve.

5. Additional costs to the owners:

The ICF should include the following:

a. Whether owners will be responsible for the cost of any treatments or diagnostics that may be necessary for the health of the animal should any adverse events occur as a result of the investigational study.

b. Other potential costs to the owner.

c. Where further information regarding costs may be obtained.

B. Description of benefits and compensation

The ICF should include:

1. Reasonably expected benefits to the animal derived from reliable information. The ICF can provide a clear and balanced description of potential benefits not only to the individual animal, but also to "others." For example, the animal's participation in the study may not benefit the animal but may benefit future patients with the same disease or condition.

2. A statement that a beneficial outcome for the study animal cannot be guaranteed.

3. A clear statement when there is no intended clinical benefit to the study animal.

4. A clear statement that, because the purpose of the study may be to determine the safety and/or effectiveness of the drug compared to a control or placebo, it is not yet known whether the drug may or may not provide a benefit and the study animal may be in a control or placebo group.

5. Avoidance of overly optimistic statements of the clinical investigation that may be misleading or represent the new animal drug as safe or effective for the purpose for which it is under investigation, which would violate FDA regulation (21 CFR 511.1(b)(8)(iv)).

6. A statement of whether any compensation will or will not be provided to the owner.

7. A description of any compensation, which may include, but is not limited to, things such as medical care, procedures, reduction of costs (for example, no charge for physical examinations), or cash payments. CVM considers payment to owners for participation in clinical investigations to be compensation for expenses and inconveniences, not a benefit of participation in the study. If payments are provided, the consent process should not identify them as benefits; however, the requirements to qualify for payments should be clearly delineated in the ICF. Compensation should not be contingent on completion of the study.

C. Statements regarding voluntary participation, involuntary termination of owner's participation, and consequences of owner's decision to withdraw

The ICF should include:

1. A clear statement that study animal participation is voluntary and that refusal to participate, or the owner's decision to terminate participation at any time, will not impact the care of the animal or involve a penalty or loss of benefits to which the owner is otherwise entitled.

2. A statement indicating the study animal may be removed from the study at the discretion of the investigator with or without the owner's consent. For example, the investigator may remove the animal from the study if the owner is unable to comply with procedures required by the protocol, if the animal no longer meets eligibility criteria for continuing in the study, or if the site at which the animal is enrolled withdraws from the study.

3. A description of any special procedures for study animal withdrawal from the study, including an explanation of any withdrawal procedures or follow-up care that are recommended to ensure the animal's safety.

4. A statement informing the owner of the requirement for study animal medical record retention when their animal is withdrawn from the study.

5. The potential consequences resulting from an owner's decision to withdraw from the study. For example, potential side effects, additional costs not compensated, or loss of veterinary medical oversight provided by participation in the study.

D. Description of procedures, treatments, and potential discomforts

The ICF should briefly discuss, in plain language, the procedures, treatments, and potential discomforts the study animal may experience, for example, imaging (radiographs, ultrasound, etc.), blood and/or urine sample collection, injections, and drug administration or application. The ICF should identify study procedures and tests that would not be part of their animal's care (for example, drawing blood samples for pharmacokinetic data).

E. Description of the risks associated with participation in the study

The ICF should briefly discuss of the following:

1. Potential risks or side effects of the use of the IVP or active pharmaceutical ingredient(s) (API) to study animals. These risks may include any safety information or relevant findings identified in pilot data, the target animal safety technical section, published literature, or publicly available reports (for example, European Medicines Agency reports). If safety information about the IVP is limited, the ICF may include safety information about the API(s), drugs in the same drug class, approved drugs containing the same API(s), or other relevant information.

2. Potential risks of the study procedures to study animals (for example, anesthesia, sedation, or surgery).

3. Potential risks of any active control products to study animals. Client Information Sheets for FDA-approved products used as an active control product are acceptable to provide to owners. Providing the owner with a copy of the package insert as the sole description of potential risks or side effects is not appropriate, as the package insert is not written in plain language.

4. Human User Safety:

   Human user safety should be considered a component of the ICF, and should include the following:

   a. A clear description of how to handle and dispose of the IVP, active control product, and any associated delivery devices, as well as any procedures to mitigate the risk to owners, if applicable.

   b. Risks from exposure before and during the administration of the test article(s), if known.

   c. A clear description of how to handle and dispose of animal bodily fluids, particularly if the IVP is to be administered at home or if special mitigations are necessary (for example, use of gloves, disposing of vomitus or waste in plastic bags). This may be especially applicable to oncology drugs, or other IVPs that maintain a high-risk profile after administration.

   d. Information regarding no contact or petting times for treated animals, if applicable. Contact between treated animals and humans or other animals is a common potential risk for dermal or topically applied products.

   e. Risks to household members from accidental exposure.

   f. A clear description of the occupational and residential risks to humans, including children and pregnant or nursing women, if applicable.

   g. Risks to human users as a result of IVP lack of effectiveness, including any zoonotic concerns (for example, ascariasis should an anti-parasiticide demonstrate a lack of effectiveness).

   h. Procedures following accidental human exposure, including directions on medical assistance, for removing the product from the eyes or skin (for example, wash contacted skin or rinse eyes), or counteragent (for example, naloxone).

   i. A statement that any reported accidental human exposure is required to be reported to the FDA by the sponsor (as defined in 21 CFR 511.1(8)(ii)).

For more information regarding Human User Safety, see draft GFI #278, "Human User Safety in New and Abbreviated New Animal Drug Applications."[9]

F. Providing significant new findings to owners

The ICF should state that significant new findings will be provided to the owner in a timely manner. It is particularly important to include this information for investigations that are complex or involve significant risk and when knowledge of potential risks is limited (for example, studies using novel therapies and new molecular entities).

Examples of significant new findings that should be provided to the owner include, but are not limited to, the following:

1. New risk information that may relate to the study animal's continued participation in the study.
2. Unexpected adverse events.
3. Adverse events occurring at greater frequency or severity than previously stated in the consent process.
4. Lack of effectiveness when it may impact the survival or well-being of the study animal.

G. Statements on confidentiality

Confidentiality is a critical element of any ICF. The ICF should clearly describe:

1. The extent, if any, to which confidentiality of records identifying the owner and animal will be maintained.
2. That there is a possibility that the FDA may inspect the records.
3. How the data generated from the study will be used by the sponsor/investigator (for example, published, reported to the FDA, etc.).
4. That the confidentiality provisions described will not be affected by the owner's decision to remove their animal from the study or by any other action, save by operation of law.

H. Signature on the Informed Consent Form

Each owner participating in the study should be required to sign an ICF. The space for the owner's signature should be preceded by an explanation in plain language of what

[9] https://www.fda.gov/media/166696/download (April 2023). When final, this guidance will represent FDA's current thinking on this topic.

the owner's signature represents.

The ICF should describe the signature as an acknowledgement that the owner has been provided the information discussed in the form. It may describe the signature as affirming the investigator has explained that:

1. Participation in the study does not guarantee that the study animal will experience any improvement in health.

2. The drug product being studied is not FDA-approved for the use under investigation.

3. The owner wishes to participate in the study and that such participation is undertaken voluntarily.

4. A confirmation that the owner is the owner of the study animal. In cases of authorized agents, the agent's identity and scope of authority should be set forth in writing, signed by the owner, and attached to the ICF upon the agent's signing on behalf of the owner.

Consider having a neutral witness present for the signing of the ICF by the owner or their agent. Consider providing a space for the witness to sign, confirming that they witnessed the owner signing the ICF.

I. List of contacts

The ICF should provide an explanation to the owner of whom to contact:

1. For answers to general questions or concerns.

2. With concerns regarding clinical signs their study animal may be experiencing.

3. In the event of a study-related injury to a study animal or owner.

4. For further explanation of the owner's rights.

VII. Informed Consent Form discussions with CVM

Informed consent may be discussed with CVM at any point in the development process, although ideally, conversations would occur before studies are conducted using an informed consent form. The sponsor's decision regarding when to start the conversation with CVM may be affected by where the project is in the development process and the information available, among other factors. CVM recommends the sponsor consider any concerns regarding animal and/or human user safety or conditions of use that may impact the ICF as early in the drug approval process as possible. CVM recommends sponsors use the initial presubmission conference process to discuss plans to address unique aspects of the new animal drug or conditions of use that may impact the ICF.

If the sponsor is seeking review and concurrence on an ICF, the ICF should be submitted at the time the applicable study protocol is submitted for review (E-submission). To allow CVM to review the ICF and provide appropriate feedback, if necessary, CVM recommends the sponsor assess the ICF for inclusion of the recommendations discussed in this GFI, as applicable, prior to submission.

CVM's Office of New Animal Drug Evaluation (ONADE) project managers (PMs) serve as a central point of contact for pioneer drug sponsors and can provide information about the new animal drug review process and ONADE's regulatory procedures. If sponsors have questions and do not have an ONADE PM assigned to their company, sponsors can contact the PMs through the CVM mailbox CVM.ONADE.PM@fda.hhs.gov.