Guidance for Sponsors on Key Provisions in Veterinary Clinical Trial Agreements in the European Union

Susan Clements provides sponsors with some useful indicators for negotiating veterinary clinical trial agreements.

This article provides an overview of contractual provisions for sponsors to consider when entering into veterinary clinical trial agreements for clinical trials in the European Union. It includes provisions on: contracting parties; clinical trial governance; obligations of the parties and the investigator; confidentiality; publication; intellectual property; and financial arrangements.

The purpose of the article is to provide sponsors with an easy-to-use guide on key provisions in veterinary clinical trial agreements. Whilst it is by no means exhaustive, it should provide sponsors with some useful indicators for negotiating veterinary clinical trial agreements.

Contracting parties

The International Cooperation on Harmonisation Guideline on Good Clinical Practice (VICH GCP)[1] that the then European Agency for the Evaluation of Medicinal Products implemented in July 2001 is intended to ensure that studies are conducted and documented in accordance with GCP principles. Whilst it is not binding, the guideline is intended to facilitate the mutual acceptance of clinical data by relevant regulatory authorities in the EU, Japan and the US[2].

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Pursuant to VICH GCP, the investigator is the individual responsible for the conduct of the study at the trial site[3] and should be qualified by education, training and expertise to perform such tasks[4]. By signing the protocol with the sponsor, the investigator agrees that the study will be conducted according to the protocol following the principles of GCP and applicable regulatory requirements[5].

The clinical trial agreement is an opportunity to make the institution responsible for the investigator and responsible for ensuring that the study will be conducted according to the protocol following the principles of GCP and applicable regulatory requirements.

The clinical trial agreement should be between the sponsor and the institution, rather than individual investigators. The institution should agree to procure the services of the named investigator or any other investigator agreed between the parties. The institution should ensure that the investigator: has the necessary qualifications, time and resources to perform the clinical trial; is made aware of and acknowledges the obligations applicable to the investigator; and performs the obligations of the investigator[6].

Clinical trial governance

Clinical trial governance is of paramount importance. Therefore, the parties to the clinical trial agreement should expressly agree to comply with all relevant laws of the EU and the member state in which the trial site is located; to comply with the study protocol; and to comply with all relevant guidance relating to clinical trials including VICH GCP.

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Obligations of the parties and the investigator

The Community Code on Veterinary Medicinal Products[7] provides that no veterinary medicinal product may be administered to animals unless a marketing authorisation has been issued for that product, except for tests of veterinary medicinal products including clinical trials, which have been accepted by the competent national authorities, following notification or authorisation in accordance with the national rules in force[8]. Therefore, the parties must not only conduct the trial in accordance with the study protocol, they must also conduct it in accordance with the clinical trial notification or authorisation granted by the relevant national authority.

It is essential that the trial does not start before regulatory approvals have been obtained. Therefore, the sponsor should not supply the investigational veterinary product to the investigator until it has received all approvals.

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It is also important to make specific provision for what happens to the IVP during and at the end of the trial. In particular, the investigator must not permit the IVP to be used for any purpose other than the conduct of the clinical trial. At the end of the clinical trial, or on its earlier termination, all unused IVPs should, at the sponsor's option, either be returned to the sponsor or disposed of in accordance with the protocol or the sponsor's instructions[9].

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It is also useful to consider timelines for the clinical trial and its associated responsibilities. These include relevant dates for regulatory approval, the start of the clinical trial and the end of the clinical trial. It is important to be realistic to ensure that timelines can be met and to provide for what should happen if there are any delays[10]. As regards capacity, the institution should ensure that the investigator does not conduct any other trial which might hinder their ability to conduct the clinical trial[11].

The sponsor should retain the ability to exercise control over the trial

As regards regulatory compliance, the sponsor should retain the ability to exercise control. In order to do so, the institution should allow the sponsor to examine the conduct of the trial and the trial site on reasonable advance notice to determine that it is being conducted in accordance with the clinical trial agreement[12]. The institution should also inform the sponsor of communications with regulatory authorities. In particular, it should promptly forward copies of any correspondence from any regulatory authority and inform the sponsor of any inspection or enquiry from any such authority. It should use all reasonable endeavours to allow the sponsor to review and amend any proposed reply and have a representative present during any inspection[13].

VICH GCP provides that the investigator must permit the regulatory authorities to inspect the facilities and trial documents for the purpose of verifying the validity of data[14]. Therefore, the institution should allow representatives of regulatory authorities access.

Pursuant to VICH GCP, it is the responsibility of the sponsor to provide a final study report[15], although it can be prepared by the sponsor, the investigator for the sponsor, or the sponsor and investigator through a collaborative effort[16]. The clinical trial agreement should stipulate which option will be used and provide that the report must be prepared on completion of the clinical trial whether prematurely or otherwise[17].

Confidentiality

The sponsor will want to keep all information confidential, including the results of the trial, in order to protect its commercial interests. It will therefore want to define confidential information widely as information given to or obtained by the institution in connection with the clinical trial. However, the institution will want to narrow the scope of this definition so that, for example, it would not cover information that the institution has before its receipt from the sponsor or in connection with the clinical trial; information that is independently developed by the institution; and information that is published other than as a result of a breach of the undertakings by the institution[18].

The institution should restrict access to confidential information to those directly concerned with the trial

In order to maintain confidentiality, the institution should restrict access to confidential information to those directly concerned with carrying out the clinical trial agreement. The institution should limit disclosure of confidential information by undertaking that it will, and procuring that its officers, agents and employees undertake that they will treat as strictly confidential and not disclose to any third party any confidential information except where disclosure is required by a regulatory authority or by law. Where disclosure is required, the sponsor should maintain at least some control over the disclosure. Therefore, the institution should inform the sponsor within a reasonable time before making the disclosure of the requirement to disclose and the information to be disclosed[19].

The sponsor should specify the ongoing nature of the confidentiality provision. In particular, that it should survive the termination or expiration of the clinical trial agreement without limit in time. It will be important to consider carefully any attempt to reduce this time period, in order to retain data and marketing exclusivity.

Publication

The sponsor may want to impose conditions if the institution is permitted to publish results

The sponsor will want to retain sole control over the publication of the results of the clinical trial. However, having defined confidentiality widely, the sponsor may allow more room for negotiation in this regard. Depending on its negotiating position, if the sponsor agrees that the institution and investigator may also publish results of the clinical trial, the sponsor should at least consider imposing certain conditions.

First, on timing, that the institution and investigator should not prepare the data derived from the clinical trial for publication before completion of the trial or when in the sponsor's opinion the trial data are adequate. Secondly, that the sponsor should have an opportunity to comment a specific number of days before submission for publication. Thirdly, that provision should be made for the sponsor's comments to be incorporated[20]. Finally, it will be important to provide the sponsor with an opportunity to protect information. For example, the sponsor should be able to request delay in publication to enable it to take steps to protect its intellectual property[21].

Moreover, the publication provision should survive the termination or expiration of the clinical trial agreement.

Intellectual property

As a general rule, the creator of intellectual property, or his or her employer, owns the intellectual property unless ownership is transferred to a third party. Therefore, an institution or an investigator will retain ownership of any intellectual property they develop unless they assign ownership to the sponsor. The sponsor should therefore make specific provision in this respect.

The institution will retain ownership of any intellectual property it develops unless it assigns ownership to the sponsor

Whilst each party may retain ownership of any pre-existing intellectual property or know-how owned by it or licensed to it, the sponsor should provide that any intellectual property or know-how generated at the trial site that relates to the clinical trial, the protocol, the IVP or any subsequently authorised product is the property of the sponsor. The clinical trial agreement should also specifically make provision for how to achieve this. In particular, it should state that the institution should promptly disclose, and should ensure that the investigator promptly discloses, to the sponsor any such intellectual property or know-how and undertakes not to use or disclose it other than for the purposes of the clinical trial agreement. Moreover, the institution should assign, and ensure that the investigator and any other relevant person assigns, the rights in relation to all intellectual property and know-how to the sponsor and does all other acts to vest the intellectual property rights and know-how in the sponsor[22].

However, the institution may not agree to such a far-reaching assignment of intellectual property and know-how. For example, it may want to at least retain intellectual property and know-how on clinical procedure and related improvements and request a carve out. The sponsor should exercise caution in this regard, particularly if the method of administration of the IVP is new.

Again, this intellectual property provision should survive the termination or expiration of the clinical trial agreement.

Financial arrangements

Pursuant to the May 1991 guideline on Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union[23], the sponsor should provide adequate indemnity for the investigator and compensation for animal owners in the event of injury or death of the animal or loss of productivity related to the trial[24].

The sponsor should provide adequate indemnity for the investigator and compensation for animal owners if the animal is injured or dies

It will be useful to consider the nature of an "adequate" indemnity. For example, whether the indemnity should extend to personal injury caused by the negligent act or omission of the institution or the failure of the institution to conduct the clinical trial in accordance with the protocol[25].

Moreover, the sponsor should consider retaining some control over proceedings. For example, by providing that the institution must inform the sponsor promptly of any circumstances likely to give rise to any proceedings and to keep it informed of developments[26]; and that the indemnity will not apply if the institution has taken any action prejudicial to the defence of the proceedings without the written consent of the sponsor[27].

It will be essential to consider the extent to which the sponsor is also required to take out insurance cover or whether an indemnity will instead suffice.

A financial schedule should be drawn up covering all issues including costs and dates for payment

As regards general financial arrangements, the clinical trial agreement should contain a financial schedule covering all financial issues including costs related to all staff and services. The sponsor should not provide any gift or consideration not contemplated by the financial arrangements set out in the agreement. Invoicing by the institution and the time in which payments must be made should be clearly set out. Moreover, the parties should make provision for the consequences of a delay in payment, for example, interest charges or for the consequences of non-payment, for example, termination.

This overview of contractual provisions is by no means exhaustive. For example, there are many other routine points to consider, such as how the clinical trial agreement can be amended and terminated; how disputes can be resolved, for example, by considering mediation in the first instance; and governing law. However, it should provide sponsors with a good starting point when negotiating veterinary clinical trial agreements in the EU.

References

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2. See Reference 1, page 2
3. See Reference 1, Point 1.18
4. See Reference 1, Point 2.4
5. See Reference 1, Point 3.2.2
6. The NHS-ABPI-BIA model Clinical Trial Agreement 2006 (mCTA) – England, albeit a model Clinical Trial Agreement for Pharmaceutical and Biopharmaceutical Industry Sponsored Research in NHS Hospitals, Clauses 2.1 and 2.2, www.abpi.org.uk/%2Fpublications%2Fpdfs%2FMCTA-ENGLAND-FINAL-OCT06.pdf

7. Consolidated Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products as amended by Directive 2004/28/EC, www.emea.europa.eu/htms/general/direct/legislation/background.htm
8. See Reference 7, Article 9
9. See Reference 6, clause 4.10
10. Guidance on use of the model Clinical Trial Agreement 2006 (see also Reference 6), clause 7.22
11. See Reference 6, clause 4.16
12. See Reference 6, clause 4.13.4
13. See Reference 6, clause 4.13.3
14. See Reference 1, Point 3.2.35
15. See Reference 1, Point 7.1.1
16. See Reference 1, Point 7.2.1
17. See Reference 6, clause 4.15
18. See Reference 6, clause 6.3.2
19. See Reference 6, clause 6.3.1
20. See Reference 6, clause 8.2 and 8.3
21. See Reference 6, clause 8.5
22. See Reference 6, clause 9
23. Eudralex, The Rules Governing Medicinal Products in the European Union, Volume 7, Guidelines: Veterinary Medicinal Products, 7AE1A , http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev7.htm#7a
24. See Reference 23, Point 4(i)
25. See Reference 6, paragraph 2, Appendix 4
26. See Reference 6, paragraph 4, Appendix 4
27. See Reference 6, paragraph 2.4, Appendix 4