

GCP and its role in veterinary clinical trials

Prof. Ted Whittam
Faculty of Veterinary Science
University of Melbourne

Introduction

Clinical trials provide data for evaluation and review of both the safety and efficacy of investigational veterinary products (IVPs). Such evaluation and review is a fundamental component of the finalisation of an application for approval to register and market a new IVP. The drug approval process depends upon the clinical trial. Evidence-based veterinary medicine (EBM) also requires output from masked, randomised and controlled clinical trials. For EBM clinical trials provide the highest-level, most reliable evidence.

The validity of high-level evidence is sometimes compromised by flaws in the underlying data. This paper proposes the regulatory framework called Good Clinical Practice (GCP) (Anon, 2001) as a potentially useful tool for validation of veterinary clinical trials conducted in Australia.

Problems and Pitfalls in Clinical Trials

The quality of clinical trial design, implementation and interpretation are factors which can impact on the application of the data produced. Both within academia and within the pharmaceutical industry there have been cases where data have been compromised by inadequacy of one or more of these three factors.

Recently, a series of 10 papers published in the journal *Anaesthesia and Analgesia* were retracted after the principle author was found to have fabricated the data (<http://www.aeditor.org/HWP/Retraction.Notice.pdf>). An editorial in *Nature* addressed the concern that academic peer review depends on trust that the authors are genuine in their submission (Anon, 2006). Although fraud is probably rare, it is the most dangerous reason for compromise of clinical trials since it is likely to markedly alter the conclusions of the trial.

More insidious but equally problematic errors include flaws in experimental design, flaws in implementation of the protocol, accidents in data entry, carelessness in data recording and poor decision making during interpretation and reporting of the study results. Both academia and the regulators have been addressing these problems, working to develop processes that decrease the risk of unrecognised errors leading to incorrect regulatory or medical decisions.

In academic veterinary medicine there has been an increasing focus on improving clinical trial outcomes and reporting. Several authors have presented methods for improvement (Baldcock, 1991; Whittam, 1999). On the human medicine side of academia, publication of the Consolidated Standards of Reporting Trials (CONSORT) (Begg, Cho et al., 1996) has led to an increase of the quality of published reports of clinical trials; for example, the adoption of the CONSORT approach was shown to have increased the quality of reporting of the method of sequence generation and masking (Plint, Moher et al., 2006). Adaption of the CONSORT statement to veterinary large animal clinical trials has very recently added to this growing focus on quality of research output (O'Connor, Sargeant et al.).

The Regulatory Pyramid

The application of regulatory standards forms a hierarchy from weak and general to strong and focused. The hierarchy of regulatory rigour has been termed the 'regulatory pyramid' (Ayres & Braithwaite, 1992). The regulatory pyramid is analogous to the evidence pyramid of EBM. To consolidate end-user confidence in the use of veterinary medicines, the consumer requires effective implementation of the registration process. Effective regulation relies on both consumer pressure for and industry acceptance of quality standards. Self imposed quality standards can be either an individual or industry lead practice. Self imposed quality standards lay the base of the regulatory pyramid for registration of veterinary medicines. However, self imposed quality standards have potential to lead to an uneven base-level quality since some sponsors apply higher standards than others. In evaluation of regulatory rigour, self imposed quality systems are usually regarded as less rigorous than enforced codes or mandatory laws.

The Role of GCP Globally

"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" (Anon, 2001).

The code for GCP provides: "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" (Anon, 2001).

The GCP guideline (Anon, 2001) is a large document which provides detailed instruction on nomenclature, trial structure, trial design, what information is required to be collected (data), data capture and recording, data processing, report preparation and archiving. Review of this material is well beyond the scope of this presentation.

The International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH) comprises full members from USA, Europe and Japan, with Australia, New Zealand and Canada having observer and contributor status. The full member countries and Canada have adopted GCP as a mandatory standard for regulatory submissions. All IVPs being developed for those markets require application of GCP to their clinical trials.

In those countries, GCP is relied upon to reduce fraud, misconduct, misrepresentation, omission and carelessness in the design, implementation and reporting of clinical trials of IVPs.

The Role of GCP in Australia

Despite no local requirement, several Sponsors have been applying GCP to their development studies in Australia for many years. The benefits accrued by these Sponsors include; improved study quality, improved ease and hence speed of review by the APVMA, applicability of the study for foreign applications and recognition of the value of Australian research teams to their international R&D "parents". The training, monitoring and auditing requirements of GCP also ensure repeated detailed contact between Sponsors, their Contract Research Organisations (CROs) and study Investigators. This contact develops

close relationships which result in long-term gains through consistent improvement in conduct of subsequent studies.

The implementation of GCP has costs; more staff for monitoring and auditing, more paperwork, physical archiving facilities, input and output qualification of computer systems and so on. Sometimes the demands of GCP can slow the development time but this should be offset by reduced regulatory delay.

Recently, for all studies conducted for determination of food-drug residues, the APVMA introduced a mandatory requirement for application of Good Laboratory Practice (GLP). Although not identical, the standards of GCP are similar to those of GLP. All Sponsors familiar with GLP would have little difficulty introducing the additional quality system of GCP.

If the APVMA were to mandate GCP for all new product applications the requirement would inevitably increase public confidence in the regulatory decision process. The requirement would ensure consistency of the application of guideline requirements, levelling the playing field for all. At the VICH and with foreign regulators, mandatory application of GCP by the APVMA would enhance our international reputation.

Conclusion

For all newly initiated clinical trials aimed to support new product applications, or application for label extensions, a mandatory requirement for implementation of GCP would benefit Australia, the APVMA and pharmaceutical industry Sponsors. These benefits would be likely to flow on to the consuming public both in reality and perception.

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