A Declaration of Helsinki for animals

PERSPECTIVE

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Abstract

This article examines the ethical principles underlying the Declaration of Helsinki as an internationally agreed justificatory framework for human medical research. The aim of the analysis is to consider the potential usefulness of these principles for defining an internationally agreed ethical 'best practice' in clinical veterinary research (CVR). It is suggested that the specific ethical responsibilities of the clinician to protect the interests of their patient when conducting medical research may be translated into the veterinary setting. Through exploring risk and harm, unproven interventions, vulnerability and informed consent, the article identifies the ethical risks of CVR. It is shown that veterinary regulators in the UK and the European Union have addressed these concerns to varying degrees; however, disagreements over the appropriateness of specific CVR practices are identified. A commitment to collaborative exploration of the benefits and challenges of implementing a Declaration of Helsinki for Animals is proposed.

Keywords animals, ethical best practice, harm, informed consent, risk, veterinary clinical research, veterinary ethics, vulnerability.

Clinical veterinary research (CVR) creates ethical challenges at all levels of the process, from the formulation of a research question to the dissemination of the results. Veterinary anaesthetists should be aware of these challenges because they may be expected to:1) conduct their own research; 2) participate in the research of others (as anaesthetists); or 3) judge the ethics of others' research as veterinary professionals. The latter responsibility is conferred when anaesthetists become members of an ethics review committee or board (ERC) or as article reviewers. Veterinary anaesthetists may encounter problems with CVR when: 1) they are expected to participate in studies which they feel are unethical; or 2) when, as reviewers, readers, observers or listeners, they encounter scientific or media reports causing moral concern.

There is currently no internationally agreed framework—such as the Declaration of Helsinki (DOH) for human medical research ethics—applied to the conduct of clinical research within the veterinary setting (Clutton 2009). Consequently, we have been asked by the editors of this journal to frame a discussion on the ethics of CVR along the lines of an adaptation of the DOH for animals. The Declaration was first adopted by the World Medical Association (WMA) in 1964, as a statement of ethical principles for medical research involving human subjects (World Medical Association 2013). In this article, the ethical principles which the DOH promotes are considered for their potential relevance and application in CVR. An overview of the current legal frameworks in the UK and the European Union (EU) is used to demonstrate the extent to which these principles have already been addressed by specific veterinary regulatory bodies. This article also responds to discussions within the Journal's editorial board regarding the adequacy and consistency of various ethical approaches within papers submitted to *Veterinary Anaesthesia and Analgesia*. We close with thoughts on the benefits and feasibility of producing and adopting a DOH for animals, as an ethical 'best practice' in CVR.

Following international outrage at Nazi medical atrocities (which were detailed during the Nuremberg trials of 1945–1946), the principle of informed consent became enshrined within medical ethics with regard to: 1) the medical treatment of human patients; and 2) their involvement in medical research practices (United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978). Since then, detailed ethical guidelines for human medical research have been developed in many countries, with some having been explored for their potential translation into the animal research setting (Ferdowsian et al. 2020). Indeed, most recently the DOH itself

has been explored for its relevance to experimental research using animals (Petkov et al. 2022). The authors argue that much of the DOH is specific to research with human subjects and thus cannot be directly applied to non-human animal experimental research. However, the paper highlights some key principles from the DOH, such as harm-benefit analysis, which are already visible within the regulation of experimental animal research in many countries (Petkov et al. 2022).

In this article we suggest that the DOH may be more successfully applied to the management of the particular ethical challenges associated with CVR than those arising in *experimental* research involving animals. We make this distinction on the grounds that the ethical principles detailed in the WMA DOH are addressed primarily to *medical physicians*, not to research scientists. Thus, it is the medical physician's ethical responsibilities to their patients when conducting medical research that we suggest may be extended to a consideration of the ethical role of the veterinary surgeon in CVR. Whilst the DOH could not allow the human equivalent of *experimental* animal research, we argue that it could encompass an ethical model of CVR which is undertaken by veterinarians under their professional oath. The potential for the application of the principles of the DOH to CVR is here explored, and illustrated through reference to existing UK and EU legislation.[1]

General principles

The general principles of the DOH define the medical physician's ethical duties to their patients and declare unambiguously, and with international agreement, that the patient's interests must be prioritized over all other concerns. Notwithstanding, they acknowledge the potential for well-conducted research to improve patients' lives, which brings research with health-improving potential into the ethical remit of medical professionals. However, the ethical legitimacy of a physician's involvement in research does not take precedence over the rights, interests, dignity and privacy of the patient even when the latter has provided full consent. Given that the physician's principal ethical duty is to protect their patient's wellbeing, those who combine medical research with medical care may only involve their patients in research to the extent that it is justified by its potential health benefits, and only when it will not intentionally adversely affect their patients' health.

In veterinary medicine, the ethical obligation of veterinarians towards animal patients is generally directed to protecting their welfare both within and outside the specific context of CVR (Royal College of Veterinary Surgeons, 2023). However, while many professional regulatory bodies maintain similar ethical principles, i.e., that veterinary professionals should prioritize animal welfare (Global Veterinary Oaths; wsava.org), this area of veterinary ethics is complex and the practicalities of consistently prioritizing animal patient interests is frequently raised (Hiestand 2022). Perhaps CVR might be one area where a clearer distinction can be made between what is and is not in the welfare interests of animal patients.

In UK and EU legislation, a clear boundary exists based on the welfare implications of CVR conducted on animal patients and the experimental use of research animals. Whilst in both cases many other animals may ultimately stand to benefit from the research, legitimate CVR procedures must, according to routine veterinary practice, intend to improve the health of that individual animal. Experimental animal research, in contrast, is characterized by intentionally reducing an animal's welfare such as through artificially modelling a disease process in a healthy animal. We suggest that through prioritizing the welfare of veterinary patients, including those who are involved in CVR, the ethical obligations of the veterinary profession towards their patients are aligned with those of the medical profession. The latter undertake medical research on humans, for their benefit, according to the DOH.

We argue further that through committing to a DOH for veterinary clinical patients there could be a more obvious, universal and visible prioritization of animal patient welfare during CVR, and that CVR might even be seen as an important example of ethical 'best practice' for the veterinary profession's activities more broadly.

Risks, burdens and benefits

In reviewing potential conflicts between human medical practice and medical research, the DOH specifically considers the risks, burdens and potential benefits of medical research to human patients. It proposes that the justification for research must be sufficiently great to outweigh any anticipated risks and burdens to research participants (see harm: benefit ratios below). It further proposes that risks must be minimized, continually assessed, managed and documented by the researcher, and that if this is not carried out then the research should not be conducted.

Vulnerable groups and individuals

In medical research involving human subjects, certain 'vulnerable' individuals and groups, such as children, adults with learning disabilities and the elderly, are acknowledged to be at increased risk of being wronged, or incurring additional harm, and so receive special protection under the DOH. Consequently, the DOH requires that under general circumstances, the use of non-vulnerable groups must always be considered before vulnerable groups, i.e. competent adults

[1] The US legislation is not over-arching so has not been referenced. In the USA, State Veterinary Licenses specify what veterinarians *can* do and set disciplinary actions. The American Veterinary Medical association sets guidance on what veterinarians *should* do, but do not act as regulators.

must always be considered before children. Furthermore, research on vulnerable patients must be limited to that which directly affects their own treatment and—as a further protection—must cause only minimal harm. The purpose of these special considerations is to prevent the exploitation of vulnerable patients in research which does not directly benefit them. We suggest that the vulnerability principle has clear ramifications for animals in CVR, since animals cannot provide informed consent, every research participant and group is arguably ethically vulnerable.

The application of a similar vulnerability principle in CVR marks an ethical boundary between using 'vulnerable' animal patients in clinical research which specifically benefits them, in contrast to research which aims to benefit other species (including humans) or those with unrelated conditions. For this reason, the European Animal Research Directive 2010/63/EU explicitly exempts non-experimental clinical veterinary practices (including CVR) from its scope (see Art. 1.5.b).

Applying the vulnerability principle in practice should limit CVR to treatments which are likely to benefit the individual, or conspecifics with similar conditions, with potential to cause only minimal harm. In the ethical analysis of CVR, it should also be recognized that some animals may be additionally vulnerable (e.g., unowned, stray or 'pound' animals).

Scientific requirements and research protocols

The DOH requires that before studies proceed, a full research protocol, including a statement of ethical considerations, funding/sponsors, insurance, consent, treatment of the research subject and conflicts of interest are declared to an appropriately constituted research ERC. Understanding the scientific principles involved and the proposed research methods is particularly necessary for establishing the harm: benefit ratio—an estimate of the degree of suffering a study participant is likely to experience compared with the benefits that are likely to accrue. The study protocol must also show that any harms have been reduced to the minimum necessary to achieve the research objectives, through the application of refined research methods.

Many potential problems arising in CVR may be avoided by a similar prospective ethics review of the study protocol (see below). From 1 September 2022, all CVR projects in the UK, i.e. those that are not considered to be either routine veterinary procedures (RVP) or experiments covered by the Animals (Scientific Procedures) Act (A(SP)A) 1986 will be subject to ethics review. Those conducting CVR outside universities or other institutes of further education are advised to seek ethics review from the RCVS Ethics Review Panel or from a recognized institutional veterinary ERC.

Research ethics committees

The DOH describes the necessary characteristics for research ERCs; they must operate transparently, be independent of the proposed research, and consist of appropriately qualified and experienced members as well as lay persons. They must consider the laws and regulations which apply to the research participants, the research location and applicable international standards. Crucially, committees may not accept standards which fall below those specified in the Declaration, even where these are not required by law.

For CVR, the establishment of ERCs is less well advanced (which may provide a further justification for pursuing an overarching Declaration for CVR). Ideally, ERCs for CVR should be an autonomous group of appropriate clinical experts, statisticians, ethicists and suitably distanced lay persons (e.g. animal owners, nurses, community members). Their aim would be to decide whether the study as applied for should progress or not, and if not, what changes are required in the study design or in some of the ethical issues. Since CVR conducted in practice is not always reviewed by research funders, the ERC would have a broad remit in assessing both scientific and ethical aspects of the study, because scientific inaccuracies will make a study less robust and thus less justifiable. An ERC must conduct an independent harm: benefit analysis in which the predicted benefits of the research (for animal health and welfare) are weighed against the potential harms for those animals directly involved in the study, their owners or other participating personnel. In addition, the harms and benefits to the veterinary profession, the institute or practice where the work is conducted, and society at large may be taken into consideration. Ultimately, all decisions would still need to satisfy relevant national animal law and national veterinary professional standards (Magalhães-Sant'Ana et al. 2015).

The independence of ERCs for CVR is critically important. For example, the members of practice-based ERCs should ideally not all be employed by those proposing the research. Similarly, institutional ERCs must resist the temptation to acquiesce to the expectations of researchers who are also part of the senior school management team. In addition, consideration should be given to appointing a person independent of the research as the animal's attending veterinarian.

Privacy and confidentiality

The privacy and confidentiality of human medical research subjects are protected by the DOH in ways which can or have been applied to CVR. For example, in the UK, ensuring that an animal owner's personal data are handled appropriately and

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that applicants are aware of personal data protection laws (e.g. the UK Data Protection Act) is one of the remits of an ERC.

Informed consent

Informed consent, as a pillar of human medical research ethics, is addressed in considerable detail within the DOH. Importantly, its detail on the process of obtaining adequately informed and freely given consent for humans involved in medical research is entirely applicable to CVR. It advises on the extent of information to be provided, the manner in which it is delivered and the significance of dependent relationships between patients and the physician/researcher in potentially influencing the decision-making process. Recently, the RCVS has suggested that ethics review be sought for all CVR which might reasonably be expected to require client consent before an animal is enrolled. However, it must be emphasized that in ethical terms, the informed consent of an animal owner and that of a human patient are not equivalent, because the former does not aim to protect all of the animal's interests (Ashall et al. 2018). Animal participants are regarded as the legal property of the owner in most countries, although the latter's wishes are generally restricted by differing legal welfare obligations. For this reason, the ethical justification for CVR should not depend on owner informed consent alone, particularly if the vulnerability principle is invoked.

This dilemma was recently exemplified by a publication in *Veterinary Anaesthesia and Analgesia* which described a prospective, randomized, blinded, placebo-controlled multisite (and multinational) clinical study of bedinvetmab in dogs with varying degrees of osteoarthritis (Corral et al. 2021). Despite valid assurances of legitimacy, including ERC approval and informed owners' consent, objections were received by the journal editors which focused on the fact that the study appeared to permit analgesic drugs to be withheld for at least 7 days in dogs with arthritic pain. The objections maintained that animal owners could not elect to withhold pain medication from their animals for research purposes, and that veterinarians should not have complied with such requests. The complainants suggested that veterinary treatment involving a drug of proven benefit should have been used as a comparator, irrespective of the owner's agreement to a treatment *versus* placebo group allocation (see below).

With regards to informed owner consent more generally, caution is particularly required when an owner's judgement may be emotionally impaired, such as in emergency or end-of-life situations. When information is only being provided by the researcher, who may be unwilling or unable to provide a balanced opinion, independent animal advocacy is appropriate.

Use of placebo

The DOH only permits the use of placebos (or no intervention) in control groups when no proven intervention exists. Therefore, control patients must always receive the best proven intervention unless under exceptional circumstances when there is no additional risk of harm. All patients involved in medical research must, as soon as possible, have access to the most beneficial intervention (as identified during their trial).

For CVR in the UK, the use of placebos must be authorized by the Veterinary Medicines Directorate (2022) through issuance of an Animal Test Certificate (ATC). This process requires confirmation that ethical approval has been given (or is being sought) from an appropriate ERC.

Research registration, publication and dissemination of results

The DOH requirement that clinical trials on humans are publicly registered in advance of patient recruitment has numerous advantages. It promotes clarity among collaborators, prevents accusations of 'p-hacking' and limits unnecessary research duplication. Importantly, by revealing study design and planned outcome measures, it promotes the publication of all results, whether they be positive, negative or inconclusive.

Reputable reviewers and editors are unlikely to publish materials which are not in accordance with the DOH. However, in CVR, this currently relies on those involved in the review and editing process being aware of ethical requirements which are normally enshrined in individual journals' guidelines for authors. One widely recognized minimal requirement for manuscript acceptance is evidence that the submitted work underwent preliminary ethical review. The International Association of Veterinary Editors guidelines (International Association of Veterinary Editors 2010) stipulate that manuscripts may be considered for publication only if they demonstrate 'best practice' in veterinary care (Point 3). Whilst best practice veterinary care is arguably context dependent, we are here proposing that *ethical* best practice in published CVR might be universally demonstrated through adherence to a DOH for animals.

Unproven interventions in clinical practice

In considering the use of unproven interventions in clinical practice, the DOH recommends that where no proven intervention exists, or where all other options have failed, a clinician may use an unproven intervention after seeking expert advice, providing the intervention offers hope of saving life, re-establishing health or alleviating suffering. The

intervention should subsequently be made the object of research establishing safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

This approach could equally apply to the EU cascade system of prescribing veterinary medicines, although this is not the case at present (European Commission 2019; Veterinary Medicines Directorate 2021). Unproven veterinary interventions more generally have not been diligently regulated and concerns have been raised for the welfare of animals receiving such interventions (Clutton et al. 2022). The UK RCVS has a Clinical Case Ethics Review Form for an applicant to complete, but it emphasizes that the final responsibility for experimental treatment must lie with the MRCVS carrying out the procedure.

A Declaration of Helsinki for animals?

In this article we have examined the DOH and considered which of its elements might be applicable to principles of ethical 'best practice' in a CVR setting. In doing so, we have sought to highlight the ethical risks of CVR and options for their management. In our opinion, through the preceding analysis of published CVR and the discrepancy in regulatory frameworks which exist in different countries, we suggest that the profession requires, as a matter of urgency, an overarching set of principles which set out universal requirements for ethical CVR.

This is complicated by numerous factors, the most fundamental of which are the cultural (and/or national) attitudinal differences that exist, both to animals in general and to certain species (Szűcs et al. 2012). According to the Global Animal Law Association, such differences affect the nature of animal welfare legislation (Global Animal Law Association 2022) which will have numerous and widespread consequences on animal production methods, animal experimentation and importantly, veterinary professional ethics, including what form a professional oath takes. Implementation of a DOH for animals as an internationally agreed best practice in ethical CVR would therefore require many veterinarians to work beyond their own legal and professional requirements in order to reach this standard.

Attention has already been paid by veterinary regulators in many countries to most of the principles outlined in the DOH, indicating that an adaptation for veterinary use does not seem wholly unrealistic. A pathway to achieving a DOH for animals might involve the collaborative writing and agreement of an International Declaration, through relevant veterinary associations and organizations, and a commitment to promoting the principles from journal editorial boards. The basis for adopting these principles internationally, however, would be an acknowledgement of veterinary ethical obligations to the animal patient, which have been argued by many to be less clearly defined than those of the (human) medical profession. Adopting a 'Declaration of Helsinki for Animals' would therefore push the boundaries of ethical veterinary approaches, both in practice and in research, towards greater protection for the animal patient. If chosen, progress along this route would be very likely to stimulate the development of other protective mechanisms for animal patients and for animals in general.

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Authors' contributions

VA: analysed Declaration of Helsinki and interpreted for relevance to clinical veterinary research, drafted the paper, collated and edited additions from other authors. DM: edited and approved the final paper, wrote elements relating to the regulation of clinical veterinary research and experimental animal research in the UK and EU. EC: edited and approved the final paper, wrote elements relating to the anaesthetists' role in clinical veterinary research and case examples from the field.

Conflict of interest statement

Authors declare no conflict of interest.

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