

The development of a national guideline to promote the wellbeing of animals used for scientific purposes

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Abstract

The *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes* is the key public policy governing the use of animals for research, teaching and product testing in Australia. The Code establishes an ethical framework for decision-making and details processes for ethical review, approval and monitoring. The Code establishes principles relating to justification and the 3Rs against which proposals to use animals must be validated and sets criteria to assess animal welfare outcomes. The nexus between animal welfare and scientific outcomes is a basic tenet of the Code. Thus, to achieve both animal welfare and scientific goals, an evidence-based approach is important when applying the principles of the Code.

The *Guidelines to Promote the Wellbeing of Animals* used for Scientific Purposes were developed to guide investigators and members of Animal Ethics Committees. They advocate consideration of an animal's 'whole of life' experiences, argue the potential confounding risk of unintended pain or distress and promote the 3Rs, pain management and humane endpoints. These guidelines provide background material about wellbeing, pain and distress, discuss strategies to identify, minimise and manage pain and distress and include a series of Fact Sheets relating to specific research procedures.

Keywords: wellbeing, pain, distress, refinement, humane endpoints

Introduction

The *Australian Code of Practice for the Care and Use of Animals for Scientific Purpose* (NHMRC, 2004), (the Code) is the key public policy governing the use of animals for research, teaching and product testing in Australia. Through the establishment of an ethical framework for decision-making and the processes for ethical review, approval and monitoring, the Code promotes the principles of Replacement, Reduction and Refinement (3Rs).

Since the Code was first considered, two foundation principles have been to avoid, or minimise, pain and distress and, in the planning and conduct of scientific activities using animals, to acknowledge the pivotal relationship between animal welfare and scientific outcomes (Rose, 2005).

An evidence-based approach is important when applying the principles of the Code so as to achieve both animal welfare and scientific goals. From time to time, guidelines which complement and inform the application of the principles of the Code are developed to address specific issues. When the use

of animals is justified, strategies which promote wellbeing and minimise pain and distress are fundamental to achieving the goals of the Code. This paper describes the development of a guide to inform the critical development and implementation of such strategies.

The Australian code of practice

The Code encompasses all aspects of the care and use of, or the interaction with, animals for scientific purposes in medicine, biology, agriculture, veterinary and other animal sciences, industry and teaching. The Code covers all live, non-human vertebrates and higher order invertebrates. Animals at early stages in their development can experience pain and distress, but this at different stages in different species. Thus, in these circumstances, the Code requires that decisions concerning an animal's welfare should be based, if possible, on evidence of its neuro-biological development.

The Code works by providing a set of ethical principles which guide decision-making on whether

or not to use animals in research, teaching or product testing. It is a hands-on document to assist investigators, teachers and Animal Ethics Committees (AECs) in their ethical judgment. Using the Code, AECs decide if the investigator has made a case to justify the use of animals and whether the 3Rs have been given due consideration when the research plan was developed.

The Code promotes animal welfare by identifying the responsibilities of all parties involved, in particular, the institution, the AEC, the Chair of the AEC, investigators and teachers. Never the less, the primary responsibility for the welfare of animals used for scientific purposes lies with the investigator. Of note, the Code embraces a duty of care that demands a genuine commitment to the welfare of animals, a respect for the contribution animals make to research and teaching and a desire to promote their wellbeing.

Further, the Code is the basis for State and Territory legislation on animal welfare and must be complied with by all institutions in receipt of funding from granting agencies, such as the NHMRC. The Australian Code also is the basis for animal welfare legislation for a number of countries in our region.

Sponsors of the Code are Australia's National Health and Medical Research Council (NHMRC), the Commonwealth Scientific and Industrial Research Organisation (CSIRO), the Australian Research Council (ARC), and the Australian Vice-Chancellors' Committee (AVCC).

The Code, first published in 1969, is a living document and has been reviewed on seven occasions, most recently in 2004. This Review is undertaken by a Working Party of nominees of the sponsor organisations together with representatives of the State and Territory Governments, the Royal Society for the Prevention of Cruelty to Animals and Animals Australia, the latter two being major national animal welfare organisations. Through the processes required under the NHMRC's Policy on Public Consultation (NHMRC, 2002), the Australian community is actively engaged in this process. The Review takes into account both scientific and technical developments as well as community views about the ethics of animal use in research and teaching. All submissions to the Review are taken into account in the drafting of the final document.

The Review of the Code is conducted under the auspices of the NHMRC which is Australia's peak body for supporting health and medical research with responsibility for providing advice to the Australian Government on ethical behaviour in healthcare and in the conduct of health and medical research. A key strategy is to promote responsible conduct and governance of research. To do this the *Australian Code for the Responsible Conduct of Research* (NHMRC, 2007b), the *National Statement*

on Ethical Research Involving Humans (NHMRC, 2007a) and the *Australia Code of Practice for the Care and Use of Animals for Scientific Purposes* (NHMRC, 2004) have been developed as national standards.

Within the Council framework, all guidelines and policy documents produced by the NHMRC are considered by Committees of Experts; community comments are sought through a process of public consultation. Final documents are approved by the relevant NHMRC committee, the National Health and Medical Research Council itself, the Chief Executive Officer and the Minister for Health in the Australian Government.

Pain and Distress - Concerning Pain and Distress, the Code sets out a number of General Principles which include the following:-

- All projects involving animals should be designed to avoid both pain and distress. Where this is not possible, pain and distress must be minimised. All animal studies must be monitored to ensure that this occurs.
- We must assume that animals experience pain and distress in a manner similar to humans, unless there is evidence to the contrary. All decisions pertaining to the research must be based on this assumption.
- Investigators must provide pain management appropriate to the species being used, the procedure to be undertaken and the circumstances under which the research will be conducted.
- The planned end point must be as early as possible to avoid pain and distress.
- Alleviation of pain and distress which has not been anticipated must be addressed promptly. This takes precedence over the completion of the project, and must be reported to the AEC as soon as possible. This may entail an amendment to the protocol, to eliminate further serious adverse events.

Development of guidelines

To support the implementation of the Code, the NHMRC has produced a number of Guidelines to address specific issues, most recently,

- *Guidelines on the Production of Monoclonal Antibodies* (2001), and
- *Guidelines for the Generation, Breeding, Care and Use of Genetically Modified and Cloned Animals for Scientific Purposes* (2006).

In 1994, the NHMRC produced *Guidelines on Minimising Pain and Distress*. This document had proven to be a valuable guide for investigators, but it was agreed that, as a priority, this should be revised to reflect changes in approach and the development of new knowledge. In deciding to

review the 1994 document, a Working Party of experts in the field was established whose brief was to make recommendations to the Animal Welfare Committee of the NHMRC.

An inaugural meeting was held to decide on the tasks required to produce a revised document.

The Working Party agreed that the purpose of the document would be to promote the wellbeing of animals and, through the identification and management of practices and procedures which adversely affect their wellbeing, to minimise pain and distress; the scope, content and focus of the revised document would reflect developments in the Code and, in particular, new knowledge in the management of pain and distress, since the 1994 publication. The Working Party recognised the need to consider not only the potential impact of specific research procedures but also the range of stresses which are part of an animal's daily living conditions and social environment - a whole of life approach. Another important consideration was how adverse effects on wellbeing may affect the validity of research results and thus the number of animals required to achieve a scientific objective. However, it was seen as important that the document should provide practical guidelines and should focus on Refinement.

The draft document developed following this meeting was approved by the Research Committee of NHMRC prior to circulation for public comment. The distribution was extensive – all research organisations, universities, research institutes, Government agencies and animal welfare organisations as well as public advertisements in the national media. Some fifty (50) responses were received which were reviewed by the Working Party and the document was revised in the light of these submissions.

In July 2007, the document was approved by the Chief Executive Officer and the National Health and Medical Research Council for publication. As with any document addressing specific issues, the new guideline must be read in conjunction with the Code.

Overview of guidelines to promote wellbeing

Given that these Guidelines were developed to assist institutions, investigators and AECs to achieve the goals of the Code to promote the wellbeing of animals used in scientific activities, the focus is on practical issues emphasising (i) promoting wellbeing, (ii) minimising pain and distress and (iii) developing strategies to effectively manage pain and distress and promote wellbeing.

Central to these Guidelines is the notion that "*The Principles of the 3Rs aim to reduce the impact of scientific activities on animal wellbeing, and are pivotal to achieving the goals of the Code. Underlying those principles is strong scientific evidence that animals experience pain and distress in a manner*

similar to humans and that decisions regarding an animal's wellbeing must be based on this premise."

The document comprises three parts: -

- A. Provides a background to assist understanding and awareness of animal wellbeing and how wellbeing relates to scientific activities.
- B. Covers the basic strategies for -
 - planning protocols to identify risk of pain and distress;
 - conducting research to manage risk; and
 - reviewing protocols to minimise pain and distress in future work.
- C. Comprises a series of fact sheets which deal with specific research protocols.

Throughout the Guidelines, relevant definitions from the Code have been selected to ensure consistency of terminology, including animal welfare, animal wellbeing, distress and pain. In defining such terms, the Code provides a framework for their use. Thus, animal welfare encompasses the different ways in which an animal may respond to its circumstances, ranging from a positive state of wellbeing to a negative state of distress. Criteria that define wellbeing and distress provide a basis for the critical evaluation of how an animal is coping in a given situation, and hence also provide evidence that informs our judgment about their welfare.

Part A – Provides a background to the document with an overview of the scientific basis for the concepts of wellbeing, stress, distress and pain. The physiological and behavioural indicators of wellbeing, stress, distress and pain are discussed and the effects of an animal's wellbeing on scientific outcomes are reviewed.

Concerning possible effects on scientific outcomes, it is noted that the aim of good experimental design is to use animals that are in a stable and defined physiological state and that, where there is not a stable baseline for reference, this can lead to incorrect interpretation of data due to the effects of a treatment being masked or confounded.

It is known that animals will experience physiological and behavioural perturbations associated with stress, distress or pain either as part of the experimental protocol, in which case the magnitude of the effect must be minimised commensurate with the aims of the study (humane endpoints). But, if incidental, causative factors should be eliminated or controlled so as not to confound data collection and interpretation of results. Thus, it is argued, in these circumstances it is in the interests of good scientific practice to maintain the wellbeing of animals used in scientific activities and to identify, control and, if possible, eliminate factors likely to cause physiological or behavioural responses associated with stress or distress.

Part B - Planning, Conducting and Reviewing Research Protocols to Maximise Wellbeing and Minimise Pain and Distress in Animals

Key issues discussed in this section relate to determining whether alternative, non-animal methods can be used, the design of projects to use the minimum number of animals to get meaningful data and predicting, minimising and managing pain and distress. Careful consideration of these issues, it is argued, will ensure that the principles of the 3Rs are embedded into the planning process; scientists using animals in scientific procedures have an ethical and legal obligation to ensure that the principles of the 3Rs are used wherever possible.

Before developing a new research protocol using animals, the Guidelines recommend that the investigator should consider:

1. whether the use of animals is justified,
2. if similar projects have been performed elsewhere, and
3. whether the same results could be obtained using tissue culture, computer modelling or other alternatives to animals.

If the use of animals is justified, there are a number of issues which need to be considered in the planning process to ensure the scientific validity of the study as well as to eliminate or reduce unwanted variability associated with the animal's living conditions and social environment. In this regard, issues which are discussed include, the choice and definition of animal models, transport, acclimatisation, housing and husbandry. The Guidelines then discuss the implications of these matters to experimental design, emphasising the importance of a well designed study to achieving the principle of Reduction.

Predicting Potential Pain and Distress: The Guidelines note that whilst specific aspects of experimental procedures may impact on an animal's wellbeing other factors such as capture, transport, handling, restraint, housing, social and physical environment, and phenotype also need to be taken into consideration when looking at potential causes of pain and distress. Further, to predict potential pain and distress requires knowledge of the husbandry and handling of a particular animal, its normal behaviour and what can be expected if the particular procedures used cause adverse effects.

The value of pilot studies in the management and planning of the research project is emphasised, recognising that they help to refine research protocols, thereby reducing the adverse impact on animals before large-scale studies are run. Pilot studies also are useful for helping to develop and refine techniques and procedures.

Noting that risk management is a stepwise process for assessing and then implementing alternatives for mitigating risks, the Guidelines suggest that such an

approach has potential application to pain and distress in animals where it could supplement the usual processes for diagnosis, prognosis and situational analysis.

Developing Strategies for Assessing, Minimising and Monitoring Pain and Distress: For each experimental protocol, to develop a strategy to assess, minimize and monitor pain and distress the Guidelines recommend that decisions are made about the following:-

- the clinical signs or observations that will be used to assess an animal's wellbeing or clinical condition as the project progresses;
- the clinical sign or combination of clinical signs that will indicate that intervention (including euthanasia) is necessary;
- the actions that will be taken if a problem is detected;
- the frequency of monitoring;
- the people who will conduct the monitoring, and their training; and
- the system for the recording of observations.

Through this process, the Guidelines highlight the need to determine appropriate points at which intervention will be necessary and to set criteria for humane endpoints. The importance of accurate documentation of the monitoring strategy, to ensure that all persons involved with the care of the animals are aware of the basis for determining the presence and severity of pain and distress also is highlighted.

Conducting the study: The management plan, developed through this process, will be validated in the conduct of a study. Although specific details will be tailored for a particular protocol, a general approach will include monitoring animals for signs of pain or distress so as to manage both predicted effects and unforeseen complications and to provide adequate pain management and palliative treatment.

The importance of undertaking a regular review of strategies to manage pain and distress so as to ensure optimum animal welfare outcomes and to implement refinement of procedures, where possible, is emphasised as is the important role of the AECs and the need to ensure the AEC is kept informed of any problems or adverse events as soon as possible.

Part C – Fact Sheets were developed to consider specific, common research procedures such as,

- Administration of substances
- Behaviour modification
- Collection of blood and other biological specimens
- Humane killing and euthanasia
- Production of polyclonal antibodies
- Surgical procedures
- Tumour Induction
- Wildlife Research

Each Fact Sheet follows a similar format including

a discussion on the purpose of the procedure, what is involved, the essential animal welfare and scientific issues and management of predicted impact. Importantly, these are living documents, intended as a guide based on current knowledge and will be regularly reviewed and updated to reflect new, relevant knowledge.

Conclusion

The *Guidelines to Promote the Wellbeing of Animals used for Scientific Purposes* were developed to guide investigators and members of AECs. These guidelines advocate consideration of an animal's whole of life experiences, argue the potential confounding risk of unintended pain or distress and promote the 3Rs, pain management and humane endpoints.

References

- NHMRC (2002) *Statement on Consumer and Community Participation in Health and Medical Research*. Commonwealth of Australia, Canberra.
- NHMRC (2004), *Australia Code of Practice for the Care and Use of Animals for Scientific Purposes*. Commonwealth of Australia, Canberra.
- NHMRC (2007a) *National Statement on Ethical Research Involving Humans*. Australian Government, Canberra.
- NHMRC (2007b) *Australian Code for the Responsible Conduct of Research*. Australian Government, Canberra.
- Rose MA (2005) The development and implementation of public policies governing the use of animals in the life sciences – influences and outcomes. *ALTEX*, 22: 80.

