June 11, 2019

Committee on the Care and Use of Dogs in Biomedical Research Funded by or Conducted at the U.S. Department of Veterans Affairs
The National Academies of Sciences, Engineering, and Medicine
500 Fifth Street, NW
Washington, DC 20001

RE: Assessment of the Care and Use of Dogs in Biomedical Research Funded by or Conducted at the U.S. Department of Veterans Affairs

Dear Committee Members,

On behalf of the Humane Society of the United States (HSUS), Humane Society Legislative Fund and our supporters, we submit these comments for consideration to The National Academies of Sciences, Engineering, and Medicine’s Committee on the Care and Use of Dogs in Biomedical Research Funded by or Conducted at the U.S. Department of Veterans Affairs (VA) ("the Committee").

The Committee has been tasked with addressing various issues related to the use of dogs specifically funded by or conducted at the VA, including whether the dog is “necessary” for any research directly related to the mission of the VA, identifying state-of-the art care standards, and evaluating the VA’s current review and oversight practices. A key issue that is not outlined specifically for the Committee but should be a part of any final report or recommendations, is whether there are evidence-based outcomes to demonstrate that dog studies have resulted in scientifically valuable information that could only be obtained by using dogs. Further, the Committee should evaluate if any findings from VA dog studies have clear relevance to human health and the mission of the VA.

The fact that dogs have been used historically as a model of human disease does not sufficiently justify their continued use. Recognizing that the agency has limited funds, the VA must prioritize the application and continued development of non-animal alternative approaches that are faster, less expensive and more relevant to human health than animal studies. There are numerous, effective alternatives to the use of dogs available and this Committee has a unique opportunity to serve as a catalyst for the integration of these alternative approaches into a health research strategy that will advance our understanding of, and ability to treat, human disease.
Animal models will always have limitations and never improve, while alternatives, through sustained development of technologies, will only continue to advance and will do so significantly. Moving the agency beyond reliance on the outdated animal models will revolutionize healthcare for Veterans and all humans. Greater transparency, including decision making processes, is vital for more effective research that translates into improved outcomes for Veterans and increased public confidence in research. Enhanced transparency in VA research is necessary regardless of the outcome of the review.

Below, we make specific recommendations for how to assess the utility of dog research at the VA, pursue non-animal approaches, increase welfare, improve transparency, and suggest criteria for judging the necessity of dog use directly related to the VA’s mission.

**Recommendations**

1. **Retrospective reviews of VA dog research**

   We recommend that the VA carry out a retrospective analysis of whether past dog use has positively impacted veteran health or was necessary for the mission of the VA. This should be done before any new research begins at or is funded by the agency. VA should be required to evaluate and report whether the objectives of the project were achieved, whether any of the information was critical in moving forward into human trials, details regarding the numbers of dogs used as well as the overall harms inflicted, and levels of pain and distress the dogs within the studies were subjected to. There should be frequent analysis to ascertain whether replacement, refinement or reduction approaches can be implemented into protocols. Where information obtained using dogs proved an absolute necessity for subsequent clinical trial(s) and could not be obtained by any other methods, the agency should further analyze whether there was translational success from dogs to humans in order to provide an objective measure of whether there were benefits of VA research using dogs.

It is important to understand if VA research is contributing to veteran health developments. Just recently Cindy Buckmaster, the chair of Americans for Medical Progress, a group that performs public outreach in support of animal research, was quoted saying “I do not support the use of animals in research of any kind whenever it is determined that their involvement is not scientifically justified. And I believe this to be true of the research community, in general.”

During the March 27, 2019 Public Workshop on the Uses of Dogs in Biomedical Research, presenters spoke about two areas of research for which VA still uses dogs, cardiovascular and spinal cord injury (SCI). However, presenters also spoke about the high failure rate of translating results of animal studies in these fields of research to humans. Dr. Igor Efimov presented about his research using donor human hearts to study cardiovascular disease. During his presentation, Efimov quoted a 2011 journal article by Robbins highlighting the problem with the copious amounts of data that have been obtained from animal studies and the “relatively tiny impact of these data on human health in general and cardiovascular disease specifically. Our ‘wet bench’
advances have not, with rare exceptions, been translated to the bedside.”

Likewise, in her presentation about large animal models for spinal cord research, Dr. Candace Floyd cited success rates in pharmaceutical research and noted the particularly low translation rate in studies of neuroprotection in SCI at ~1%. With rates this low, it seems likely that a comprehensive retrospective analysis of dog use in VA research will reveal problems with using live animal models and the need to pursue non-animal methods as described in more detail below and in the appendix.

Where dogs are being used in VA research, we urge the agency to carry out a retrospective meta-analysis of the research outcomes as part of ongoing efforts to replace the use of dogs. The analysis should consider the actual, cumulative harms inflicted on the dogs over the duration of the research project and quantify the realistic, actual benefits of the research. This should enable calculation of the translational efficacy of dog research in order to enable decision making over the continued use of dogs versus alternatives.

2. Pursue the use and development of alternative methods

Instead of relying on the historical use of dogs as a justification for continuation of these practices, HSUS urges serious consideration of non-animal alternatives via dedicated, ring-fenced funding in order to support more human-relevant advances that will signify a firm commitment from the agency to move away from dogs. It is hard to deny the pace at which the new approach methodologies are advancing – microfluidics were only introduced to in vitro culture methods in the early 2000s, and less than 20 years later, development of arrays that link several human organ systems are commercially available for PBPK modelling in early drug discovery studies. However, the technology is available for much more than just toxicology and drug discovery and the capacity of these, and other, advanced in vitro systems in disease modeling is increasing. Importantly, the National Institutes of Health (NIH) have demonstrated their commitment to these advanced non-animal technologies, with several funding initiatives totaling over 72 million dollars for the development of organs-on-chips, including the Disease Chips Program which is supporting, amongst others, a project using chips to test novel treatments for atrial arrhythmias. We recommend that the Committee hears from the leaders in these fields, who we name and whose research we discuss more extensively in the appendix, to explore the possibilities of replacement and to better appreciate how the replacement of a large animal model will require integration of more than one in vitro/in silico approach.

There could be significant financial advantage to shifting away from dogs—animal research is very costly at every level—from the financial outlay required for the animals, costs incurred in their upkeep, training of researchers and caretakers to the ultimate likelihood of a novel, safe and

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5 https://ncats.nih.gov/tissuechip/funding
effective treatment. The widespread acceptance and mainstream use of *in vitro* methods has led to some analyses of their cost and reveal that the *in vitro* methods are often more cost-effective than using animals. Add to this the incredibly low translation rates for animal-based research and the physical, financial and psychological costs incurred by Veterans awaiting treatments and it becomes preferable, in fact vital, to see research funds going towards the creation and application of *in vitro* and other non-animal approaches. We urge the VA to reconsider any decisions regarding the possible replacement of dogs with another sentient species, such as pigs, and instead to invest in the development, promotion and application of human relevant non-animal approaches such as those detailed in this appendix.

We would like to emphasize that, there are no simple like-for-like replacements such that a single *in vitro* assay will stand in for an animal model. We do not see this as a reason to continue using the animal models, or to spend scant research resources ‘tweaking’ existing animal models to create something symptomatically similar to a human condition.

We have specifically considered the research fields of particular interest to the VA, namely cardiovascular and spinal cord injury and present our detailed findings on where we see opportunities to move away from animal models in the attached appendix.

To summarize the main points of our appendix, the VA should:

- Incentivize and promote the use of human tissues and organs;
- Promote and further develop the use of patient registries to share data and enable best practices to be disseminated among VA research facilities;
- Explore computer modeling of organ function and response to perturbations, including drug treatment or disease processes;
- Investigate partnerships with veterinary clinics to increase participation in veterinary clinical trials;
- Exploit existing *in vitro* methods to investigate cellular function and response – these should include the types of sophisticated, three dimensional models of tissues which are revolutionizing the field and which may incorporate cell scaffolds, multiple cell types, dynamic flow systems and bioprinting to develop more complex, physiologically relevant structures; and
- Where intact organisms are deemed necessary, investigate alternative models of lower sentience such as slime molds or zebrafish embryos.

In addition to recommending a general move away from the use of dogs, we urge this Committee to recommend that the VA formalize a strategy and/or roadmap for the development of non-animal alternatives and a commitment to ending the use of dogs as soon as possible in support of the agency’s mission. We also strongly recommend that the VA join The Interagency.

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9 Meigs et al Animal testing and its alternatives - the most important omics is economics. ALTEX. 2018;35(3):275-305. doi: 10.14573/altex.1807041.
10 Kramer and Greek Human Stakeholders and the Use of Animals in Drug Development. 2018 Business and Society Review 123:1 3–58
Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Here they can optimize the utilization of scientific expertise within, as well as outside of the US federal government. In the future, the VA can work with key members of other federal agencies that have been at the forefront of efforts to further carry out the 3Rs of reduction, refinement and replacement with the ultimate aim of replacing animals with more human relevant approaches.

3. Welfare enhancements

If the results of this review indicate that Committee recommends the continued use of dogs in VA research, the agency should consider adopting higher welfare standards for dogs than the current laws and guidelines require. The established requirements in the Animal Welfare Act (AWA) and the Guide of the Care and Use of Laboratory Animals (the Guide) outline the bare minimum animal welfare standards.

In his presentation to the Committee, David DeGrazia outlined his ‘basic needs’ for dogs used in research. The HSUS and HSLF agree with these principles and suggests that the Committee ensure that all these needs are met in any VA dog research protocol that may be deemed necessary: sufficient rest for health; access to compatible dogs or social group members; freedom from significant experiential harm; freedom from disease, injury, disability and freedom of movement with adequate space. We have specified the basic needs that we feel are the minimum requirements to adequately meet research dogs’ needs in our criteria, outlined below.

The statement of task asks the Committee to identify ethical standards and state-of-the-art practices supporting the care, use and welfare of dogs in research. The VA can establish a gold standard of care for dogs in research, with enhancements to exercise and enrichment requirements, safer flooring and improved socialization of animals. A recent study, The influence of facility and home pen design on the welfare of the laboratory-housed dog\(^\text{11}\), highlights that modifications to current requirements and recommended standards promote more positive welfare of dogs in laboratories. Additional considerations can be taken from the EU Directive 2010/63/EU\(^\text{12}\) in which minimum space requirements are based on weight, with at least 2 square meters per animal (US is approximately one-third of this). Another significant difference between EU and US requirements is the minimum height. In the EU this is 2m, irrespective of dog size, whereas the AWA only requires 6 inches above a dog’s head. The EU Directive also states that dogs should not be single housed for more than 4 hours and should have access to an outside run “where possible”. We would urge the VA to adopt these more stringent, more humane requirements for any dogs used in their research program until such a time as those dogs can be adopted.

Finally, the HSUS applauds the agency for having a publicly available adoption policy but encourages the Committee to further improve this policy by requiring VA research facilities that use dogs in research to establish partnerships with reputable animal rescue groups to facilitate the placement of adoptable animals. The HSUS already partners with the VA to help facilitate the placement of adoptable animals.

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adoption of shelter pets to Veterans and would be pleased to offer assistance in identifying respectable organizations to aid in the adoption process. Adequate support and socialization of dogs leaving a research facility are necessary for successful placement in a forever home, to minimise any distress to the animal, safeguard the public and reduce the chances that the dogs are returned to the shelter.\(^{13}\)

The HSUS is proud to have established a strategic partnership with the VA to support Veterans, their well-being, and their social integration through the adoption of rescued animals and related interactions with companion animals. In this collaboration, we work with the VA to promote and expand pet keeping for Veterans, encourage their engagement with local animal shelters and other humane organizations as adopters, patrons, and volunteers, and communicate the many benefits that companion animals bring to the lives of Veterans throughout the nation.

4. Improving Transparency in Research Requiring Dogs

The Committee should recommend that VA research facilities receive annual USDA Animal and Plant Health Inspection Service (APHIS) inspections and that the documented reports of these inspections be posted publicly to the USDA database. We remain concerned that the frequency and robustness of internal inspections are not sufficient in the protection of animal welfare at VA research facilities. A 2014 audit from the USDA Office of Inspector General (OIG) found that IACUCs “did not adequately approve, monitor, or report on experimental procedures on animals\(^{14}\).” OIG reviewed Animal Welfare Act (AWA) violations from FYs 2009 – 2011 and found that 531 of 1,117 research facilities were cited for 1,379 IACUC oversight violations.

Due to Congressional concern over USDA’s Agricultural Research Service (ARS) in 2015, a Memorandum of Understanding\(^{15}\) was entered into which established annual APHIS inspections at ARS facilities to help ensure adequate oversight. APHIS should also carry out rigorous, unannounced inspections at VA facilities. With many similar concerns at VA facilities, inspections by APHIS will provide increased animal welfare protections as well as provide much needed transparency by the agency.

All staff involved in animal research, and in the breeding, housing and care of laboratory animals, must be properly trained and supervised. Training records should be available for inspection by APHIS inspectors and should provide part of the inspection report available for public scrutiny. Adequate training and education are vital if the VA is to demonstrate effective alignment with 3Rs principles, since knowledge obtained through training can address animal welfare needs, recognition of pain and distress and appropriate housing\(^{16}\).


Where dogs are being used in research, the experimental design should be registered in agreement with proposals put forward by NASEM Committee member Dr Jonathan Kimmelman.\(^\text{17}\) We suggest that pre-registration of all studies requiring dogs would be a powerful tool to reduce publication bias, improve transparency, prevent duplicative research and holds true to the principles of the 3Rs. Records could be made publicly available, after a grace period to ensure that no intellectual property rights are breached. It may be possible for researchers to use an adaptation of the study proposal already submitted to the IACUC as the pre-registration document. Pre-registration of preclinical studies should improve the credibility of research and can be used to improve standards of animal research\(^\text{18}\), where animals are still required. The VA could offer funding to facilitate pre-registration of any studies requiring dogs, and it is possible that Dr Kimmelman could explore what this might entail with the Committee. However, we note that there is a freely available, international preclinical trials registry available at [www.preclinicaltrials.eu](http://www.preclinicaltrials.eu) and so compliance with this recommendation may not require significant financial outlay.

5. **Adopt similar principles and criteria to the Institute of Medicine’s report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*\(^\text{19}\).**

The conclusions of this 2011 report were driven by advances in models and methods other than the use of chimpanzees. The Committee developed three principles to assess research on chimpanzees and additional criteria for determining the necessity for using chimpanzees in biomedical research. We recommend that this Committee develop similar principles and criteria for the use of dogs in research at the VA. The principles and criteria listed below should be adjusted for the purpose of this study; namely, to ensure the research is directly related to the mission of the VA and, further, addresses the need to enhance the welfare of dogs currently in VA laboratories, until such time that dogs are no longer deemed necessary for VA research or the VA makes a decision to end the use of dogs.

### Principles Guiding the Use of Chimpanzees in Research

- The knowledge gained must be necessary to advance the public’s health;
- There must be no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects; and
- The animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats.

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\(^{18}\) Ritskes-Hoitinga & Wever. Improving the conduct, reporting, and appraisal of animal research. BMJ 2018;360:j4935 doi: 10.1136/bmj.j4935

Criteria for Use of the Chimpanzee in Biomedical Research

1. There is no other suitable model available, such as in vitro, non-human in vivo, or other models, for the research in question;
2. The research in question cannot be performed ethically on human subjects; and
3. Chimpanzees are necessary to accelerate prevention, control, and/or treatment of potentially life-threatening or debilitating conditions.

The Committee should require, if research using dogs is deemed necessary and in the context of the VA’s mission, that the following criteria are met in order to permit research using dogs:

- The knowledge gained must be novel, of benefit to wider society and necessary to advance understanding of issues associated with the health of Veterans.
- There are no other suitable models, or combinations of models, available, in this order of priority: non-animal methods, including but not limited to, in vitro (cell lines, primary cells, organoid cultures, microphysiological systems, stem cells), in silico (mathematical modeling of existing data sets, computational modeling), ex vivo methods (tissue slices, explant cultures), in vitro models employing animal cells or animal tissues, human volunteers, or, where all other possibilities have been exhausted, another animal model. Where research questions cannot be answered by one or more of the non-animal methods, the necessity for using whole animals should be clearly justified and the use of immature forms (embryos) or invertebrates should be considered. In general, VA research should commit to the use of the least sentient organism, as per currently available scientific information, including but not limited to Dictyostelium discoideum\textsuperscript{20}, Caenorhabditis elegans\textsuperscript{21}, Lymnea stagnalis\textsuperscript{22}, and zebrafish\textsuperscript{23}.

- The study cannot be performed ethically using human subjects.
- The dogs used in the proposed research must have all of their ‘basic needs’ met including, but not limited to, the needs delineated by Dr. David DeGrazia:\textsuperscript{24}
  - Nutritious food & clean water;
  - Appropriate shelter;
  - Adequate stimulation, exercise, opportunities for canine-typical functioning to promote good health and psychological wellbeing in all animals including access to outdoor runs;

\textsuperscript{22} Crossley et al., A two-neuron system for adaptive goal-directed decision-making in Lymnaea. Nat Commun. 2016 Jun 3;7:11793.
\textsuperscript{23} Bradford et al., Zebrafish Models of Human Disease: Gaining Insight into Human Disease at ZFIN. ILAR J. 2017 Jul 1;58(1):4-16.
\textsuperscript{24} http://nas-sites.org/dels/files/2019/04/David-DeGrazia-Presentation.pdf
• Sufficient rest for health;
• Veterinary care;
• Access to compatible dogs or social group members ensuring dogs are not single-housed for more than 4 hours at a time;
• Freedom from significant experiential harm;
• Freedom from disease, injury, disability; and
• Freedom of movement with adequate space.

• The dogs should never be subjected to unnecessary harm including through negligence or lack of care in handling, transport, housing, etc.

• Where it is felt that research necessitates the use of dogs, by encouraging collaboration between their laboratory animal veterinarians and companion animal veterinarians to utilize the rise in veterinary clinical trials25, the VA should first consider the use of client-owned animals enrolled in clinical trials instead of requiring purpose-bred research animals.

• Researchers have consulted with statisticians to design experiments with greater measurement precision, improving the signal-to-noise ratio of the data analysis and enabling a reduction in the number of animals required and should not rely on power analysis to calculate required numbers of animals. They should also consider the most appropriate statistical analysis to ensure that all studies using dogs are reproducible26.

• The research does not pass the upper limits to harm27. There is no current standard in US law that restricts the amount of harm an animal used in research may experience. The VA should adopt a similar policy to the European Directive 2010/63/EU:
  “… the performance of procedures that result in severe pain, suffering or distress [that] is likely to be long-lasting and cannot be ameliorated should be prohibited”28 (art. 23).

• The researchers must use the least number of animals that will clearly answer the question posed and take every practical step to avoid pain, distress or suffering.

Conclusion

Given the special relationship Americans have with dogs, it is vitally important that deliberate consideration be taken when choosing when, how, and under what circumstances the use of dogs in medical research will be allowed. It is the Committee’s responsibility to ensure that all alternatives are carefully considered and should push the VA to support the development and use of human-relevant, non-animal approaches. These new technologies offer the most promise in

understanding human disease, while also eliminating the ethical concerns of animal research. At
the same, the utmost care should be given to ensure that any continued use of dogs considers
their specific needs and is done with an eye to full transparency.

Thank you for the opportunity to comment on the Committee’s important work. We welcome the
opportunity to answer any questions or provide additional information.

Sincerely,

[Signature]

Kathleen Conlee
Vice President
Animal Research Issues
The Humane Society of the United States