

# VA Canine Research Documents

## Submitted to National Academies of Science

Contract 36C25E18C0058, Assessment of the Care and Use of Dogs in Research Funded by or Conducted at the U.S. Department of Veterans Affairs

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### List of Appendices:

1. Veterans Health Affairs Handbook 1200.07. Use of Animals in Research, November 23, 2011 (under revision). [http://www.va.gov/vhapublications/ViewPublication.asp?pub\\_ID=2464](http://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2464)
2. Veterans Health Affairs handbook 1058.01. Research Compliance Reporting Requirements, June 15, 2015. [http://vaww.va.gov/vhapublications/ViewPublication.asp?pub\\_ID=3116](http://vaww.va.gov/vhapublications/ViewPublication.asp?pub_ID=3116)
3. Animal Component of Research Protocol (ACORP), Version 4. The standard VA animal research protocol form, put in use in 2015. Main body and 9 Appendices. [https://www.research.va.gov/programs/animal\\_research/documents.cfm#docs-a](https://www.research.va.gov/programs/animal_research/documents.cfm#docs-a), in the ACORP Version section.
4. VA Semiannual Evaluation of the Institutional Animal Care and Use Program and Facilities, updated for 8<sup>th</sup> edition of *Guide*. Parts 1 A/B, 2, and 3. [https://www.research.va.gov/programs/animal\\_research/documents.cfm#docs-a](https://www.research.va.gov/programs/animal_research/documents.cfm#docs-a), in the Semi-Annual Review Forms section.
5. Office of Research and Development Guidance Document AR2018-001. *Adoption of Research Animals Covered by the USDA Animal Welfare Act Regulations*, June 27, 2018; [https://www.research.va.gov/programs/animal\\_research/Guidance-adoption-USDA-species.docx](https://www.research.va.gov/programs/animal_research/Guidance-adoption-USDA-species.docx)

6. Selected VA Research Accomplishments with Dogs, 1960-Current Decade, with example manuscripts.
7. Office of Research and Development Guidance Document AR2017-001 revision 2. *Canine, Feline and Non-Human Primate Research Protocols*, October 25, 2018; [https://www.research.va.gov/programs/animal\\_research/CanineFelineNHP.pdf](https://www.research.va.gov/programs/animal_research/CanineFelineNHP.pdf)
8. Current VA dog projects
9. Veterans Health Administration FOIA Guidance on Animal Research Requests, January 30, 2013.

## **A. Brief Overview of VA Animal Research.**

The Department of Veterans Affairs was created in early form in the 1920s following the need to address chronic injuries sustained by soldiers in World War I. After successive consolidations in the 1930s and reorganizations in the 1940s, the VA received a tremendous increase in funding as a result of the need for expanded medical care for returning WWII Veterans and the GI Bill, which passed in 1944. The scope of biomedical research projects began to expand beyond the focus on tuberculosis and mental health research conducted in the late 1940s to a variety of research projects involving animals, resulting in animal research programs at over 100 VA facilities by the early 1960s. Public and agency concern about animal welfare and the lack of consistent animal care standards for research animals, coupled with the expanding number of animal research programs, prompted the VA in 1962 to establish the very first chief veterinarian position in a federal agency, termed the Chief Veterinary Medical Officer (CVMO). VA has since continued to lead the animal research community in innovative practices that both protect the welfare of research animals and encourage life-saving advances in medicine that Veterans need and deserve:

- 1960s-1970s: Veterinarians trained in laboratory animal medicine are recruited to provide support for VA animal research programs, and animal technicians were encouraged to seek training in laboratory animal care in programs like the one created by the American Association for Laboratory Animal Science (AALAS).
- 1971: A nationwide onsite training course for VA animal facility supervisors was created and staffed, which continued until the 1990. This provided course hands-on training in the specialized care needed for laboratory animals.
- 1975: Nation-wide reviews of the animal component of research grants considered for VA funding, after the protocol has been reviewed by the Institutional Animal Care and Use Committee (IACUC). Funding is not released until the CVMO approved the animal protocol. This additional VA review of the animal protocol form has been continuous performed and is now termed the “Secondary Veterinary Review.”
- 1995: To meet regulatory training mandates, VA funded a five-year training program to produce CD-based materials for animal research personnel. This program transitioned to the creation of a website that eventually provided the software platforms for the AALAS Learning Library and the CITI Program, which are web-based learning platforms for learning regulatory and ethical concepts in and animal and human research.
- 1999: All VA programs were required to be accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). All VA animal research programs have been continuously accredited by AAALAC since then.
- 1999: The CVMO’s office designed a website to organize and archive key animal research data from VA medical centers that conduct animal research.
- 2002: As part of mandatory training, VA instituted a requirement that all personnel performing animal research pass web-based courses that covered a variety of topics from individual species needs to IACUC approval requirements to training for IACUC members themselves.

## B. VA Organizational Structure.

The VA has a headquarters building located near the White House, which is termed “VA Central Office” or “VACO.” The three principal components of VA are the Veterans Benefits Administration (VBA), the National Cemetery Administration, and the Veterans Healthcare Administration (VHA). The VA medical facilities found across the nation are collectively referred to as “field” or “local” programs to distinguish their programs from VACO programs.

VHA is the largest integrated health care system in the United States, providing care at 1,243 health care facilities, including 172 VA Medical Centers and 1,062 outpatient sites of care of varying complexity to over 9 million Veterans enrolled in the VA health care program. All healthcare and research activities are within VHA. Within VHA are two offices that play a critical role in VA research:

- Office for Research and Development (ORD) <https://www.research.va.gov/default.cfm>. This office is responsible for reviewing requests for research funding and disbursing VA research dollars based upon a peer-review scoring system very much like the NIH peer review system. It is also responsible for developing and implementing policies for monitoring and conducting human, animal, bench, epidemiology, and other forms of research, and providing research subject matter experts for consultation with field programs as needed. The VA research budget in FY2018 was about \$720 M, and funds about 2,200 projects a year. The largest part of this budget supports biomedical research. The VA funding program is an internal one focusing on diseases and conditions of Veterans, and only VA researchers are eligible for funding. This contrasts with the NIH system of sending most funding to external institutions. On average 40% of funded VA studies include an animal research component. The office of the CVMO is in ORD.
- Office of Research Oversight (ORO) <https://www.va.gov/oro/>. This office promotes the responsible conduct of VA research for the protection of Veterans and others who volunteer in VA research, and for the benefit of all Veterans whose health and well-being are improved by the discoveries made through a sound and ethically grounded VA research program. ORO monitors, reviews, and investigates matters of research compliance that involve VA research. Specifically, ORO provides oversight of compliance with VA and other Federal requirements for the protection of human research subjects, laboratory animal welfare, research safety, research laboratory security, research information security, and research misconduct.

Of the 172 VA medical centers in the field, about 120 conduct some form of human research, and 72 conduct animal research, which is down from about 100 VA medical centers that conducted animal research in 1962.

Each VA medical center has a Director, who functions as the Chief Executive Officer and Institutional Official for animal research, if the facility has an animal research program. The local research department within the medical center (or “hospital”) is termed the “Research Service”, and is led by a physician or PhD scientist with the title of Associate Chief of Staff for Research and Development, often abbreviated “ACOS/R&D.” The ACOS/R&D serves as the

supervisor for the entire local research program. The animal research program refers to collectively the VA animal facilities (often referred to as the “Veterinary Medical Unit”, or “VMU”), and all the administrative and veterinary care support structures required for modern research:

- Directly supervising the daily operations of an animal facility is the Animal Facility Supervisor, who must have experience and training in laboratory animal care.
- An Attending Veterinarian (AV) with experience and training in laboratory animal medicine must be appointed for each animal facility to provide clinical support for the animals, further direction and management of the animal facility, and advice to local researchers on how to minimize the pain and stress of proposed animal research. About 10 of the VA Attending Veterinarians are federal employees have the title “Veterinary Medical Officer” (VMO) while the rest are almost all university veterinarians under contract with the VA, and have the title “Veterinary Medical Consultant” (VMC). Although there is not a direct supervisory link between the CVMO (n ORD) with local (field) VA veterinarians, there is significant communication and consultation between them.
- Each program must be monitored by an Institutional Animal Care and Use Committee (IACUC), which must be composed of individuals with specific roles and backgrounds (e.g. Attending Veterinarian, non-scientific member, non-affiliated member, scientist with animal research experience). The IACUC can be administered by the VA medical center (internal IACUC) or by the academic affiliate’s IACUC (external IACUC).

There is considerable complexity in the relationships between VA and affiliate university animal research programs. Most VA programs have their own IACUC and own animal facility, but there are many permutations of integration. For instance, some VA programs utilize a university IACUC and some even utilize the university animal facility for VA research. The nature of these relationships are defined in a written agreements. The complexity of these relationships have an impact on how animal usage is reported to USDA because animal purchased by VA could be housed at an affiliate and reported on the affiliate’s USDA Annual Report instead of the VA Report.

### **C. Collaborative Relationships with Affiliated Universities, and Funding Sources.**

In understanding the collaborative relationships between VA medical centers and affiliated university programs, it is important to realize that almost all VA Principal Investigators have appointments in affiliated university departments.

Close associations with academic university affiliates have always been an important part of VA’s medical and research mission. According to the VA Office for Academic Affiliations, VA is profoundly important to US health-professions education, having affiliations with over 1800 schools and programs in place. Nearly 124,000 trainees receive supervised clinical education in VA facilities each year with about 70% of all U.S. physicians having some VA

clinical experience in the course of their education. VHA is the second largest funder of Graduate Medical Education, after the U.S. Center for Medicare and Medicaid Services.

In addition to competing for VA funding (\$720M total budget in FY2018), there are many other competitive sources of funding VA investigators successfully utilize, including:

- Other federal funds (NIH, NSF, DOD)
- Charitable foundations (American Heart Association, American Cancer Association)
- University Departmental Funds
- VA Non-Profit Corporations (many VA medical centers have associated non-profit corporations that can receive non-VA funding)
- State Funds
- Pharmaceutical and other private funds

Collectively, VA field research programs received an additional \$570M in research funding from the non-VA sources listed above.

#### **D. VA Animal Research Regulatory Environment.**

Like most institutions that conduct animal research in the United States, VA animal research is required to comply with the following:

- Animal Welfare Act Regulations and Standards, administered by the United States Department of Agriculture (USDA AWAR), including the Animal and Plant Health Inspection Service Policy Manual [per Animal Welfare Act, 1966 as amended].

VA animal research programs are not visited by USDA inspectors but do file USDA annual reports of animal usage for USDA species.

- Public Health Service Policy on Humane Care and Use of Laboratory Animals, administered by the Office of Laboratory Animal Welfare (OLAW), NIH, including the *Guide for the Care and Use of Laboratory Animals* and the Frequently Asked Questions guidance section of the OLAW website [Health Research Extension Act of 1985].

The VA has an agreement with OLAW to provide regulatory services to VA even when particular VA programs do not have any activities utilizing PHS funds ([https://grants.nih.gov/grants/olaw/references/mou\\_olaw.htm](https://grants.nih.gov/grants/olaw/references/mou_olaw.htm)).

- American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals: 2013 Edition.

In addition, VA animal research programs are required to comply with the following internal VA policy documents:

- VHA Handbook 1200.07. Use of Animals in Research, November 23, 2011 (under revision), included as Appendix 1. This document provides requirements for conduct of VA research and self-reporting of deficiencies to internal and external entities, in a few cases extending beyond what other federal regulations and policies require.

- VHA Handbook 1058.01. Research Compliance Reporting Requirements, June 15, 2015, included as Appendix 2. This document provides requirements for internal self-reporting of animal research deficiencies to ORO, and includes guidelines for Research Compliance Officers who monitor local research and report directly to medical center Directors.

Participation in the animal research accreditation program maintained by AAALAC is voluntary for most institutions, but has been required for all VA animal research programs since 1999. AAALAC performs site visits of every VA animal research program every three years, funded by a VACO contract that covers all visits. VA programs that conduct dog research on the premises also receive a targeted AAALAC site visit of canine research in between the usual AAALAC site visits.

## E. Local Conduct and Review of Animal Research.

**1. Local Review and Approval of Animal Research.** Research is defined as VA research when VA funds are used to purchase animals, research is performed on VA property, or when VA personnel on VA tours of duty participate in the research, no matter where the location. In modern times, A VA IACUC is expected to review animal research that fits any of these criteria.

Per federal regulation, no animal research may be conducted until it is reviewed and approved by the local VA IACUC. In the VA system, proposed animal research must first also receive approval from the local Research and Development Committee, which reviews the entire research project for scientific merit and congruence with VA's medical mission of serving Veterans.

VA programs that have their own IACUC (an internal IACUC) are required to utilize the standard VA animal protocol form, which is historically termed the "ACORP", for Animal Component of Research Protocol (included as Appendix 3). Some selected items of special interest are listed:

- a. Harm to benefit analysis, item B:

**Description of Relevance and Harm/Benefit Analysis.** Using non-technical (lay) language that a senior high school student would understand, briefly describe how this research project is intended to improve the health of people and/or other animals, or otherwise to serve the good of society, and explain how these benefits outweigh the pain or distress that may be caused in the animals that are to be used for this protocol.



- b. Justification for number of animals requested, item C.2.b:

**b. Justify the group sizes and the total numbers of animals requested.** A power analysis is strongly encouraged; see ACORP instructions.

- c. Justification for the species requested, item D:

**Species.** Justify the choice of species for this protocol.

- d. Qualifications and training of personnel, item E:

**Current qualifications and training.** (For personnel who require further training, plans for additional training will be requested in Item F.)

e. Endpoint criteria, item T:

**Endpoint criteria.** Describe the criteria that will be used to determine when animals will be removed from the protocol or euthanized to prevent suffering. (Use Appendix 9 to document any "departures" from the standards in the *Guide* represented by these criteria. Consult the IACUC or the Attending Veterinarian for help in determining whether any "departures" are involved.)

f. Consideration of alternatives, prevention of unnecessary duplication of studies, and documentation of database search for alternatives that could replace animals, reduce the number of animals used, or refine procedures to better minimize pain or stress, item W:

**Consideration of Alternatives and Prevention of Unnecessary Duplication.** These are important to minimizing the harm/benefit to be derived from the work.

1. Document the database searches conducted.  
List each of the potentially painful or distressing procedures included in this protocol.

Collectively these items on the form prompt the investigator to explain why the research is medically and scientifically important, provide a justification for using animals, provide a justification for using the specific species proposed, and show that alternatives to using animals are not appropriate or available.

Thus, animals cannot be used if that research can instead be performed with alternate approaches such as cell culture, computer simulations, "organ on a chip" preparations, or other similar in vitro or in silico techniques. The use of dogs must be justified, which particular attention paid to other species that could possibly substitute for dogs. The CVMO's office conducts an independent review of the items, as detailed in Section I.

**2. Semi-Annual IACUC Reviews.** Twice a year the local IACUC is required to inspect the animal facility and also review the entire animal research program. This is a very detailed process that is documented in writing. Internal VA IACUCs must use the standard VA form specifically designed to facilitate the process, included as Appendix 4 in this document.

**3. Adoption of Dogs.** VA policy is that all dogs that can be adopted into a loving home must be (see Appendix 5). Most VA canine protocols require a terminal surgery or procedure for tissue harvest at the conclusion to obtain necessary data, so few dogs are actually available each year for adoption. In FY2017, 4 of 4 VA dogs eligible for adoption were adopted. The final data are not available for FY2018.

**4. Support for Local Programs.** In support of local programs, the CVMO's office provides in-person animal research and IACUC training for VA personnel at least twice a year at major national meetings such as the Public Responsibility in Medicine and Research (PRIM&R) meeting and the American Association for Laboratory Animal Science (AALAS) meeting. IACUC training exercises are also developed quarterly to help local IACUCs maintain expertise and remain aware of emerging issues in protocol and program review. Thirty of these exercises are available on the training page of the VA animal research website ([https://www.research.va.gov/programs/animal\\_research/required\\_training.cfm](https://www.research.va.gov/programs/animal_research/required_training.cfm)).



## **F. Additional VACO Review of Proposed Animal Research.**

Prior to August 2017, all proposed animal research submitted as part of a request for VA funding received a “secondary veterinary review” by the Office of the CVMO after the local IACUC reviewed and approved the protocol. Only after the CVMO’s office approved the proposed animal protocol would funds be released and the work allowed to begin locally.

In August of 2017 the CVMO’s office expanded the secondary veterinary review to include all proposed research involving dogs from any funding source (See Section C above for examples of other funding sources). A guidance document communicating the expanded scope of the secondary review was published on December 18, 2017 on the VA animal research website

([https://www.research.va.gov/programs/animal\\_research/CanineResearchProtocols.pdf](https://www.research.va.gov/programs/animal_research/CanineResearchProtocols.pdf)), which was then subsequently revised to reflect the request by then-Secretary David Shulkin that he personally review and approve any new proposed dog research, which was codified by Congress in Section 245 of the FY 2018 Consolidated Appropriations Bill that contains the VA budget:

“SEC. 245. None of the funds appropriated or otherwise made available by this Act may be used to conduct research using canines unless: the scientific objectives of the study can only be met by research with canines; the study has been directly approved by the Secretary; and the study is consistent with the revised Department of Veterans Affairs canine research policy document released on December 18, 2017: *Provided*, That not later than 180 days after enactment of this Act, the Secretary shall submit to the Committees on Appropriations of both Houses of Congress a detailed report outlining under what circumstances canine research may be needed if there are no other alternatives, how often it was used during that time period, and what protocols are in place to determine both the safety and efficacy of the research.”

The legislative language in Section 245 appears as Section 247 in the FY 2019 VA appropriations bill (Energy and Water, Legislative Branch, and Military Construction and Veterans Affairs Appropriations Act, 2019), so the conditions remain in place.

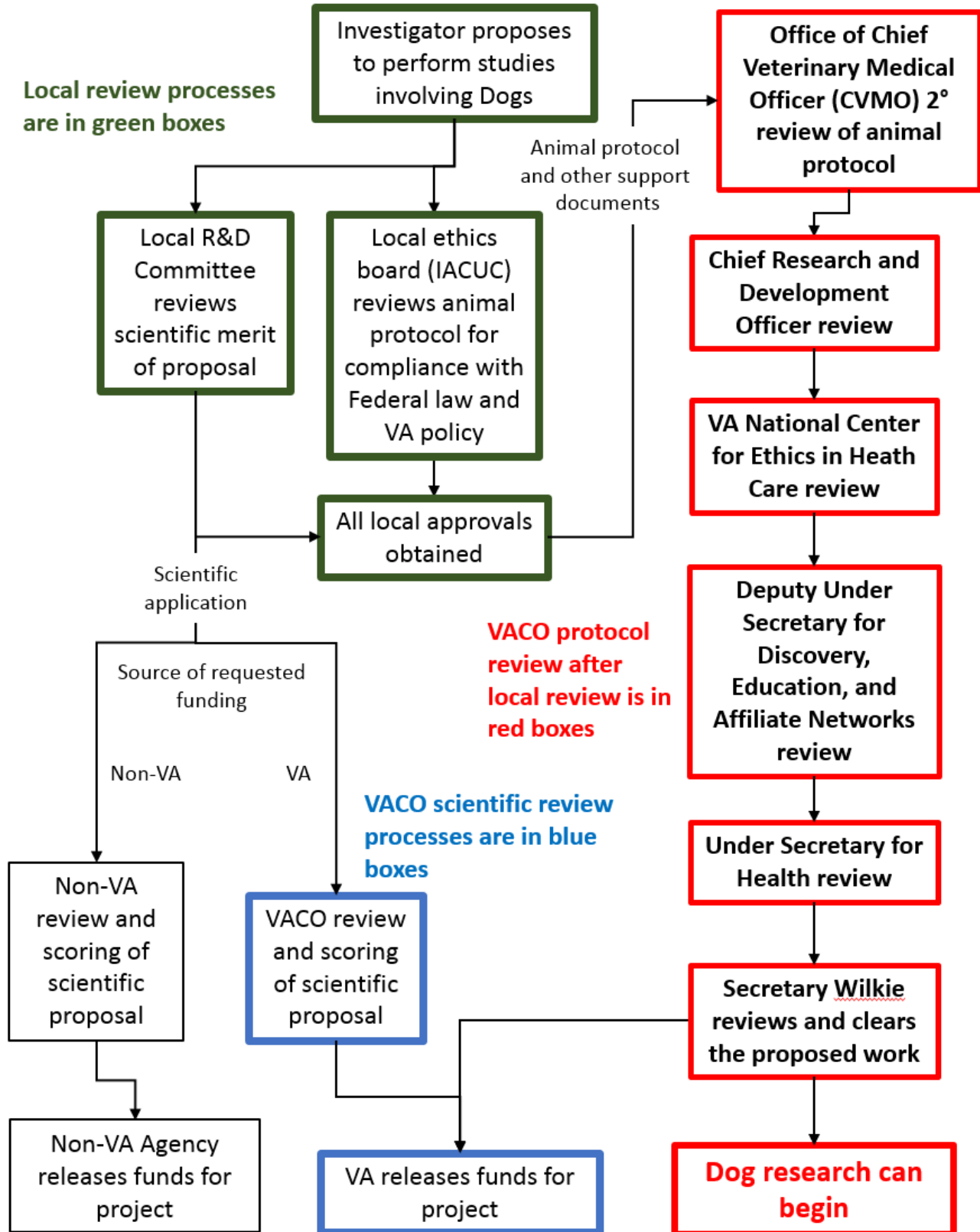
The current version of the December 18, 2017 guidance document referenced in Section 245 and 247 is Revision 2, which is included as Appendix 7 in this document. The guidance was expanded in May 2018 to cover cats and nonhuman primates in addition to dogs.

### *Current Secondary Veterinary Review Process per Revision 2*

The review process now in place is shown in the diagram on the next page. The local review processes are in green boxes and consist primarily of the local R&D Committee and the local IACIC (whether internal or external). If the dog protocol is part of a request for VA funding, the VA Office of Research and Development performs a peer-based scientific review of the scientific application very much like the one performed by NIH (blue boxes). The red boxes

show the VACO review of the animal protocol and other supporting documents, starting with the CVMO office review.

## Canine Research Review Processes after July 1, 2017 (VA and Non-VA Funding Sources)



## G. Overview- Role of Canines in VA Animal Research.

It has always been VA policy that the use of dogs in research had to be specifically justified, and the stringency of the justification has increased steadily over time, as will be discussed later. Mirroring changes in the larger biomedical research community, the number of canines used in VA research has declined. In 1995, 50 of 85 VA animal research programs reported the collective use of over 1500 canines in research to the United States Department of Agriculture. For Fiscal Year 2018 (October 1, 2017 to September 30, 2018), only 4 VA programs utilized canines in biomedical studies.

The final FY2018 dog research tally is not yet available, but the number of dogs collectively used in VA research is expected to be less than 100. This would be about 0.15% of all dogs used in the United States for research, based upon the 64,707 figure reported for FY2017 by USDA ([https://www.aphis.usda.gov/animal\\_welfare/downloads/reports/Annual-Report-Animal-Usage-by-FY2017.pdf](https://www.aphis.usda.gov/animal_welfare/downloads/reports/Annual-Report-Animal-Usage-by-FY2017.pdf)).

Based upon data reported internally provided by field programs as part of the annual web-based report required by the CVMO's office, the species breakdown in FY2017 for all VA animal research is shown below. Note that 58 of 177 the dogs reported were part of a study matching service dogs with Veterans with PTSD, and thus only 119 of the dogs were actually dedicated to biomedical research projects:

Species	Fiscal Year 2017	FY2017 % of Use
Mice	389,974	93.075%
Rats	26,309	6.279%
Voles	474	0.113%
Rabbits	456	0.109%
Hamsters	133	0.032%
Frogs	1,050	0.251%
Swine	220	0.053%
Fish	0	0.000%
Dogs	177	0.042%
Guinea pigs	58	0.014%
Primates	17	0.004%
Cats	35	0.008%
Chickens	0	0.000%
Gerbils	48	0.011%
Sheep	17	0.004%
Chinchillas	0	0.000%
Goats	22	0.005%
Cows	0	0.000%
	418,990	100%

Accordingly, 119 dogs out of a total of 418,990 animals (0.042%) were used in VA biomedical research in FY2017. To further put the figure of 119 dogs in perspective, according to a 2018 analysis by Rowan and Kartal (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5981279/>), over 775,000 dogs are euthanized each year in shelters, which is over 2100 per day. Therefore in one entire year, VA is using less than 6% of the dogs euthanized in U.S. shelters in a single day. This point was recently made by VA Secretary Wilkie in his speech to the National Press Club, as part of a very strong statement of support of VA canine research when it is needed to help Veterans:

<https://www.c-span.org/video/standalone/?c4759984/sec-wilkie-dog-research-comments> .

To summarize, canine research is an extremely small component of VA animal research. Although very small, we will document that it is scrutinized at an intensity no other institution, Federal, public, or private, comes close to duplicating. As will be documented in the next section, it has led to many

medical advancements, with great importance to Veterans and non-Veterans alike.

## **H. Earlier VA Research Using Canines.**

An early important medical advance developed from VA canine research was the successful implantation of the self-contained cardiac pacemaker by a VA surgeon and others in 1960, which has removed the early death sentence of heart disease for millions of Americans. Starting with this achievement, Appendix 6 documents historical medical and scientific advancements due to VA dog research.

Appendix 6 consists of a table of each canine research project. For each numbered project, a short summary of the work and why it was important is included with a selected manuscript documenting VA's role in it. This list is by no means exhaustive, but illustrates the large contribution of VA dog research to scientific and medical advancements for Veterans and non-Veterans alike.

## **I. Current VA Research Using Canines.**

Appendix 8 provides information on the dog protocols active as of November 15, 2018.

On June 1, 2017, there 13 active VA dog protocols across the agency (Projects 1-13 in the Appendix 8 Table of Dog Projects). In early March 2018 the VA Office of Research and Development performed a detailed re-review of all 13 protocols and recommended continuation of 9 them (Projects 1-9 in the table). Then-Secretary Shulkin approved the 9 on March 28, 2018, thus authorizing the use of FY2018 funds for these projects per the requirement in Section 254 of the FY2018 Consolidated Appropriations Bill.

As of November 15, 2018:

- Projects 1, 6, 7, 8, and 9 are still active.
- Project 3 was completed in September of 2018, and is now closed
- Project 2 is a clinical trial of bladder cancer treatment in privately owned pets being seen at the UC Davis School of Veterinary Medicine. This study is currently postponed.
- Project 4 is currently inactive due to the retirement of the PI, who is publishing remaining data. No further studies will be performed unless reviewers require them.

For each study in the table, the following documents are provided:

- The animal protocol form approved by the local IACUC and the CVMO's office.
- The feedback document ("Secondary Review") provided by the CVMO's office used by the local IACUC to develop the final approved version of the animal protocol form. This feedback is provided by at least one boarded laboratory animal veterinarian and reviewed by the CVMO, also a boarded laboratory animal veterinarian.
- A summary of the literature search done by the CVMO's office as part of the review. A PhD scientist with special training in database and literature searches does an independent literature review, and summarizes key points in this document.

Fundamentally, the purpose of the CVMO's review is to ensure that appropriate care will be provided to all dogs, that Names and other sensitive information are redacted per VA policy found in Appendix 9.

#### **J. Final Comments.**

VA will be happy to provide other documents needed by the committee to their review.