



## Research Article

# Dog as the Experimental Model: Laboratory Uses of Dogs in the United States

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### Abstract

Dogs are the experimental model in many types of biomedical research. Each year, hundreds of publications report the use of dogs in invasive biomedical procedures, often without sufficient explanation of the purpose and justification for selecting dog as the experimental model. The European Union requires detailed reporting of animal use that includes research purpose, but animal use reporting in the United States, overseen by the USDA, does not require this information. The ability to replace dogs with alternative models begins by understanding how they are used. Therefore, this study was undertaken to investigate the types of invasive biomedical procedures that dogs are subjected to in US laboratories. Well-defined sets of research publications and grants were accessed to obtain information on the types of biomedical research using dogs. USDA databases provided additional information. An ontology to categorize biomedical research uses of dogs identified the most common as translational studies for cardiovascular, cancer, nervous/mental, and musculoskeletal disorders. Information typically reported for experimental animals was sometimes missing or incomplete in publications, including the number, source, fate, species justification, and pain management of dogs, suggesting that many journals have not adopted the ARRIVE guidelines on animal use reporting. It was not possible to identify the research purpose for all dogs used by US institutions because (a) not all dog use is published and (b) animal research purpose is not required reporting in the US. These findings should be informative to future initiatives to replace, reduce, and refine the use of dogs in research.

## 1 Introduction

Americans think of dogs as pets or companion animals, often considering them valued members of the family. Most are unaware of how extensively dogs, both mongrel and purebred, are used for behavioral and biomedical research, product development, toxicological testing, and education and training purposes (Barthelemy et al., 2019; Box and Spielmann, 2005; Hasiwa et al., 2011; Ikeda-Douglas, 2005; Lee et al., 2018; NASEM, 2020; NRC, 2009a; Powers and Recchia, 2018; Wilson et al., 2020).

Although many research studies involve the use of computational, molecular, and cellular models, animal models are still a mainstay of biomedical research. To protect the welfare of animals, most governments have enacted laws and regulations.

The United States enacted the Animal Welfare Act (AWA) in 1966. The United States Department of Agriculture (USDA) was charged by Congress with the task of administering the AWA, and implementation was assigned to USDA's Animal and Plant Health Inspection Service (APHIS). The AWA "establishes requirements concerning the transportation, sale, and handling of certain animals... Regulations established under the AWA set standards for the humane care and treatment for certain animals that are exhibited to the public, sold for use as pets, used in research, or transported commercially"<sup>1</sup>. The *Guide for the Care and Use of Laboratory Animals* (NRC, 2011) and the *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (NIH OLAW, 2015) are additional resources guiding the use of laboratory animals in the US. As part of implementing

**Disclaimer:** The National Anti-Vivisection Society (NAVS) opposes the use of dogs in biomedical research and product testing for both ethical and scientific reasons.

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<sup>1</sup> [https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/awa/ct\\_awa\\_program\\_information](https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/awa/ct_awa_program_information) (accessed 02.24.2022)



the AWA, APHIS collects annual statistics on the types and numbers of animals used by licensed research facilities in the United States, although some common laboratory species such as rats and mice are excluded.

Information on the purpose of laboratory animal use and the number of animals used for various types of research is essential for understanding trends in animal use and for identifying research areas that should be prioritized for the development of alternative research models. Annual statistics on the use of dogs for research by institutions in the United States are reported to USDA-APHIS. USDA-APHIS reports only minimal animal use information, which includes the number of animals used, for certain species, and the number per species subjected to various levels of painful procedures<sup>2</sup>. The purpose or type of research involving the use of dogs is not part of US reporting requirements. In contrast, animal use data are reported annually in the European Union (EU) with far more detailed reporting requirements that include the research purpose and number of animals per species<sup>3</sup>. Non-technical summaries are also provided to make the information accessible to the public<sup>4</sup>. Animal use data and reporting requirements of the EU are important to consider, even when studying US data, as the EU's more comprehensive data collection and animal use regulations might inform new opportunities for reducing animal use in other countries or regions<sup>5</sup>. Whereas the number of dogs used annually for research in the US has remained steady over the past several decades at around 60,000 dogs per year<sup>6</sup>, it has declined in the EU from around 27,000 dogs used in 1991 to around 15,000 per year (2015-2018)<sup>3</sup>. This represents a substantially lower use of dogs in the EU considering the EU's larger human population, but direct comparisons are complicated by a number of variables such as the number of EU Member States covered in European reports changing over time and possible differences in the types of dog use covered in the different government reports.

Considering how common and accepted it is to use dogs in research, there has been little effort to document the types of research using dogs and an often-insufficient effort to examine the rationale for selecting dog as the experimental model. Hundreds of research articles from US institutions and dozens of review articles are indexed annually in the PubMed database reporting the use of dogs in biomedical research, but few publications were identified that more broadly explain the use of dogs in contemporary biomedical research. One example is the summary findings from an international workshop held in 2011 on the use of dogs in biomedical research, safety assessment, and drug development in Europe, which reported EU statistics on dog use and the limited results obtained from a survey on severity, pain, and number

of dogs used in experimental procedures (Hasiwa et al., 2011). Even with limited data, those authors compiled some useful recommendations and concluded that because “*methods to fully replace the use of dogs and other animals are not available yet*” it is desirable in the meantime to reduce the number of dogs and refine dog care and experimental procedures (Hasiwa et al., 2011). Among the many review type articles explaining the use of a dog model for a particular type of research or procedure, a review article on dog models for neuromuscular diseases stands out by providing additional discussion on the history of dog use in biomedical research as well as describing dog use reported in the US versus EU (Barthelemy et al., 2019). This paper also addresses ethical issues related to using dogs for research and explains many of the justifications made for dogs being the “optimal system” in preclinical studies for translational research.

As part of the response to growing public and scientific concerns over the use of dogs in biomedical research in the US, the use of dogs in research funded or conducted by the US Department of Veterans Affairs (VA) was examined by an expert panel established by the National Academies of Sciences, Engineering, and Medicine (NASEM) (NASEM, 2020). Several divisions within the National Academies have been involved for decades in providing guidance on the care and use of animals to US researchers and institutions (NRC, 1994, 2009a,b, 2011). The NASEM panel's report found that “*using laboratory dogs in research at the...VA is scientifically necessary for only a few areas of current biomedical research*”<sup>7</sup> and recommended actions the VA can take to reduce and replace dogs in research. The VA was also instructed to work collaboratively with other organizations to identify and develop alternative methods to replace the use of dogs in biomedical research.

For this study, a review of well-defined sets of recent grants and publications was conducted to identify information on the use of dogs in biomedical research by US institutions. Dog use data was procured from three sources that report research involving the use of dogs by US institutions: (1) research publications indexed in the National Library of Medicine's PubMed database, (2) National Institutes of Health (NIH)-funded biomedical research grants, and (3) USDA databases. The results of this study provide information on the types of invasive biomedical research being conducted using dogs and the types of research using the greatest number of dogs, and they identify deficiencies in animal use reporting practices in research publications. While the grants are required to report all of the types of animal use data needed for this study, the research publications were often missing some of the information, indicating that journals are not following the guidance on animal use reporting for publications

<sup>2</sup> [https://www.aphis.usda.gov/library/forms/pdf/APHIS\\_7023.pdf](https://www.aphis.usda.gov/library/forms/pdf/APHIS_7023.pdf)

<sup>3</sup> European Commission. Animals Used for Scientific Purposes: EU Statistical Reports on the Use of Animals for Scientific Purposes. [https://ec.europa.eu/environment/chemicals/lab\\_animals/reports\\_en.htm](https://ec.europa.eu/environment/chemicals/lab_animals/reports_en.htm)

<sup>4</sup> European Commission. Animals Used for Scientific Purposes: ALURES Statistical EU Database. [https://ec.europa.eu/environment/chemicals/lab\\_animals/alures\\_en.htm](https://ec.europa.eu/environment/chemicals/lab_animals/alures_en.htm)

<sup>5</sup> Abbott, A. (2020). Animal-research data show effects of EU's tough regulations. *Nature.com*. doi:10.1038/d41586-020-00352-6

<sup>6</sup> USDA-APHIS (2021). Research facility annual summary & archive reports.

[https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa\\_obtain\\_research\\_facility\\_annual\\_report/ct\\_research\\_facility\\_annual\\_summary\\_reports](https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_obtain_research_facility_annual_report/ct_research_facility_annual_summary_reports) (accessed 05.22.2021)

<sup>7</sup> NASEM (2020). Dogs necessary for only a few areas of research at veterans affairs; Agency should adopt expanded criteria for using dogs.

<https://www.nationalacademies.org/news/2020/07/dogs-necessary-for-only-a-few-areas-of-research-at-veterans-affairs-agency-should-adopt-expanded-criteria-for-using-dogs>

provided by the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines<sup>8,9</sup>. The ability to identify the research purpose for all, or even most, of the dogs used in the US was not possible from publicly available sources because (a) not all dog use is reported in scientific publications and (b) government-required reporting of animal use in the US does not include the reporting of research type/purpose. The findings from this study will help define initiatives to replace, reduce, and/or refine (the 3Rs) the use of dogs in biomedical research. Reaching this 3Rs goal would not only address concerns about the use of dogs in research but would also facilitate faster and more human-relevant drug and device development, which at this time often relies on the use of dog data.

## 2 Methods

### *Scientific publications reporting the use of dogs*

The PubMed database was the source for identifying scientific publications reporting the use of dogs in biomedical research<sup>10</sup>. Boolean operator-based searches with various combinations of search terms were used to maximize identification of relevant articles indexed in PubMed, while minimizing irrelevant ones. To obtain the most current but complete 12-month dataset, articles published in 2018 were selected for data collection and were identified using the search terms “(dog OR canine) AND 2018 AND (USA OR United States).” The final search, conducted in January 2020, identified 1,809 articles. Many of the full-length publications were available from direct links in PubMed to the journal or the PubMed Central archive. When the full-length article was not available through PubMed, it was obtained from a library or by making a direct request to one of the authors. It is important to note that PubMed was completely rebuilt on a new technology platform that replaced the legacy platform in May 2020<sup>11</sup>, and the original search that identified 1,809 articles now identifies a slightly larger set of articles (2,091 as of May 1, 2021). Also note that the inclusion of *Canis familiaris* (used in the RePORTER search described below) was examined as a PubMed search term but not used because it identified only additional articles that were not relevant to this study.

“Inclusion criteria” were defined and used to vet articles for relevance to this study. To be considered relevant to this study, a publication (a) was identified in the PubMed search noted in the previous paragraph, (b) described an invasive procedure involving the use of dogs (“invasive” as defined below), AND (c) was authored by a principal investigator (PI) from a US institution with or without US government grant funding, OR was au-

thored by a foreign PI and US-based co-author with US government grant funding. Criterion “c” was optimized to identify dog use studies involving US institutions.

“Invasive research” for the purpose of this study is defined as any procedure that inflicted real or potential physical harm on the dog with no, or unknown, benefit to the dog. For example, studies that anesthetized, conducted physically invasive procedures, tested an investigational drug or device, or killed dogs, were considered invasive. *In vitro* or *ex vivo* studies that involved euthanizing dogs for the procurement of primary cells or tissues, or procuring them from commercial sources, were considered invasive. Examples of noninvasive studies that were excluded from data collection include: use of dog cell lines, collection of stool and/or blood samples (apart from sequential blood tests in drug studies), comparisons of approved veterinary treatments, and dog clinical case reports. Veterinary clinical studies were included when dogs were subjected to experimental treatments with unknown benefit to the patients.

Articles identified in the PubMed search were vetted for relevance using the “inclusion criteria” defined above. The first 453 articles out of the 1,809 articles published in 2018 (25%) were vetted for relevance, and 97 of the 453 articles (21%) met the study’s “inclusion criteria.” The number of articles to be screened for relevance was not preselected but was determined by the opposing constraints of time available for data collection and the need to sample a sufficiently representative number of articles. Each of the 97 publications identified for data collection was read manually to obtain the dog use data reported in this study.

### *NIH grants reporting the use of dogs*

The NIH RePORTER database was searched to identify NIH-funded grants that proposed the use of dogs in some type of biomedical research study<sup>12</sup>. The database was searched at the end of July 2019 for 2018 and 2019 grants (18-month period) using the keywords dog, canine, or *Canis familiaris*. This search identified 679 grants, and invasive research using dogs was suggested in 358 of those abstracts. NIH RePORTER does not provide the full grants, so requests for the 358 grants were submitted using the NIH Freedom of Information Act (FOIA) portal<sup>13</sup>. Responses to FOIA requests typically took months, and some NIH institutes/centers limited the number of grants to five per request. Additional FOIA requests could not be submitted until previous requests were fulfilled. As a result of this lengthy procedure, 107 of the 358 grants requested were not received by the conclusion of this study, and 61 were excluded by NIH FOIA correspondents for either not involving invasive dog research or requiring extended redaction negotiations with the PI<sup>14</sup>. Therefore, limited

<sup>8</sup> <https://arriveguidelines.org/>

<sup>9</sup> <https://arriveguidelines.org/resources/author-checklists>

<sup>10</sup> <https://pubmed.ncbi.nlm.nih.gov/>

<sup>11</sup> New PubMed transition FAQs. <https://support.nlm.nih.gov/knowledgebase/article/KA-05275/en-us>

<sup>12</sup> <https://projectreporter.nih.gov/reporter.cfm>

<sup>13</sup> <https://foiaportal.nih.gov/app/Home.aspx>

<sup>14</sup> Department of Justice Guide to the Freedom of Information Act. Procedural Requirements. pp. 62 and 68. <https://www.justice.gov/oip/page/file/1199421/download>



content for 190 grants was received, and these were vetted for relevance to this study using the previously indicated definition for “invasive research.” This resulted in 118 grants identified as relevant for use in this study.

#### *Data collection and analysis: Publications and grants*

Data from research publications and NIH grants meeting the study’s inclusion criteria were collected into Excel spreadsheets. Each publication or grant was read thoroughly by one of the authors to determine whether it met the inclusion criteria and to collect the dog use data. The types of data collected from publications and grants included: research category, research subcategory, species to benefit, species justification(s), dog number, dog breed, source of dogs, and fate of dogs. Following the input of data into spreadsheets, the data were sorted and analyzed. Analysis included determining the percentage of publications or grants per data category.

Additional information was collected from the publications on their reporting of pain management procedures. Due to the variety and complexity of pain management procedures (Carbone, 2012; Herrmann and Flecknell, 2019; NRC, 2011), it was not feasible to collect and analyze researcher explanations provided for pain management as part of this study. NIH grant proposals are required to include detailed information on the management of pain and distress for the use of any vertebrate animal<sup>15</sup>, but this type of information was commonly missing from the research publications. Therefore, publications were assessed for whether or not they reported pain management procedures for dogs. A few publications included detailed information, but most, if they reported pain management at all, included what could only be considered as partial or incomplete information (or perhaps incomplete implementation). Therefore, whether a publication explained pain management procedures for the experimental animals was categorized as “clear,” “vague/incomplete,” “missing”, or “not needed.”

Although the publication and grant data are presented together in this study, they are not directly comparable. The timeframes selected for data collection were to obtain the most current datasets. Most of the NIH grants span multiple years, and their resulting publications, if any, would appear in PubMed over various later years. Therefore, any time frame selected for grants and publications would not provide directly comparable data, which could only be obtained by following the publication output of a select number of grants over many years.

#### *Research categories and subcategories*

The type of biomedical research identified by “research category” and “research subcategory” is a primary way to categorize the purpose of a research study. A search was made to identify an existing or standardized ontology, nomenclature, or classification system for identifying “research categories” that could be used to categorize the types of biomedical research in which

dogs were used as the experimental animal. The many classification systems developed for clinical, medical, or other scientific applications were found to be too complex, and sometimes not sufficiently relevant, for the purpose of this study to more generally identify the type of biomedical research involving the use of dogs. Some of the ontologies examined include: Biomedical Topics, Ontology for Biomedical Investigations, National Cancer Institute Thesaurus, Medical Subject Headings (MeSH), Medical Dictionary for Regulatory Activities Terminology (MedDRA), and Human Disease Ontology<sup>16</sup>. The USDA is tasked with collecting annual data on the use of animals in the US, but it does not collect detailed animal use information and so does not use a defined set of “research categories.” However, the set of “research categories” and “research subcategories” already in use by the European Union to categorize animal research for EU statistical reporting requirements was found to be applicable to categorizing the research reported in the grants and scientific publications used for this study (EC, 2012, 2020a,b).

A simplified version of the EU nomenclature was adopted for use in this study. Three “research categories” were used to categorize the type of biomedical research conducted involving the use of dogs in publications and grants: basic research studies, translation/applied research studies, and regulatory use. The type of research described by each publication and grant was further categorized by one of 12 “research subcategories” (Tab. S1<sup>17</sup>). Unlike the EU system, “regulatory use” studies were additionally categorized using the 12 research subcategories rather than according to the type of toxicological test. Publications and grants each describe a number of procedures/tests, so the “regulatory use” classification by test was not applicable to this study.

#### *Dog use reported in USDA databases*

Information on the number of dogs used for research by US institutions was obtained from information available on the USDA website<sup>6</sup>. This information, which is reported annually to the USDA, is broken down by number of dogs used per state and by pain category.

A direct data request was submitted to the USDA to obtain information about USDA-licensed research institutions that used dogs. These data included the number of dogs used per pain category per institution for fiscal year 2018 (Oct. 2017–Sept. 2018).

## **3 Results**

### **3.1 Dog use reported in publications and grants**

Twenty-five percent (453/1,809) of the 2018 articles indexed in PubMed and reporting the use of dogs by US institutions were vetted for relevance to this study. Out of these 453 articles, 97 (21%) were found to involve some type of invasive research using dogs. The tabulated results are summarized and discussed in the sections below. The remaining articles vetted as not relevant

<sup>15</sup> <https://olaw.nih.gov/guidance/vertebrate-animal-section.htm> (accessed 09.09.2021)

<sup>16</sup> <https://bioportal.bioontology.org/ontologies>

<sup>17</sup> doi:10.14573/altex.2109101s



**Tab. 1: The number and breed of dogs used in the research reported in 97 publications and 118 grants**

Dog breed	Publications		Grants	
	Number of publications	Number of dogs	Number of grants <sup>a</sup>	Number of dogs <sup>a</sup>
Beagle	24	795	30	1,790
Beagle	3	not provided	3	not provided
Beagle and other breed(s) or mongrels	10	428	6	368
Hound or hound mix with or without other breeds	6	110	13	412
Mongrel and/or mix of breeds	23	327-361	19	1,205 (one not provided)
Golden retriever	2	26		
Boxer	1	1		
Australian labradoodle	1	12		
American bulldog and breed not provided	1	11		
German shepherd and hovawart	1	5		
Miniature dachshund			2	80
Irish setter			1	20-25
Labrador retriever			1	67
Genetic mix of pure breeds (varied)	3	53	3	132 (one not provided)
Breed not provided	20	189	30	1,450-1,452
Breed and number not provided	2	not provided	10	not provided
Totals	97	1,957-1,991 plus "not provided"	118	5,524-5,531 plus "not provided"

<sup>a</sup> Grants were selectively provided and also redacted by NIH, so grant data may not represent the exact distribution.

to this study either did not involve US institutions or did not involve an invasive procedure.

The NIH RePORTER database was used to identify funded grants that proposed the use of dogs as the experimental model over an 18-month period (Jan. 2018-July 2019). The 190 grants obtained through FOIA requests to NIH were vetted for relevance, and 118 were used to extract the data reported in this study. The results are summarized in the sections below. A limitation to the NIH grant results is that only a subset of the grants indicating the use of dogs was provided by NIH for this study, and some of them contained redacted sections.

### 3.2 Dogs used: Numbers and breeds

The "number of dogs" used in a procedure or study is a basic type of information needed to fully describe the experimental methods. Approximately 2,000 dogs were used in the experimental studies reported in the 97 research publications identified as relevant to this study (Tab. 1). The 97 publications represent 25% of the 2018 publications, so extrapolation to the entire year provides an estimate of 8,000 dogs. More than 5,500 dogs were proposed for experimental use in the 118 grants included in this

study, but due to the way the grants were provided (see Methods) a time-period for the use of this number of dogs cannot be assigned. Five publications and 15 grants did not provide the number of dogs used, and the number of dogs used was sometimes difficult to ascertain. Dog numbers were sometimes mentioned in different sections of the research articles, numbers in different sections did not always agree, and in several cases numbers were found only in a supplemental file or table legend. NIH requires the reporting of experimental animal number in grant submissions<sup>15</sup>, so the number of dogs must have been redacted when not found in the grants.

The total number of dogs used in research by 328 US institutions and reported to USDA-APHIS for FY2018 was 59,312 dogs (Tab. 2). The slightly higher number of 59,401 found in USDA's *Annual Report Animal Usage by Fiscal Year report for 2018*<sup>6</sup> was attributed by APHIS to animal care auditing resulting in an amended annual report (P. Osenkowski, personal communication, June 23, 2020). Twenty-four of the 328 institutions in the 2018 Annual Report used more than 500 dogs each (data obtained by FOIA; not shown). The use of 59,312 dogs by US institutions in 2018, as compared to the 8,000 estimated as being

**Tab. 2: USDA-APHIS statistics on number of dogs used in research by 328 USDA-licensed institutions for FY2018**

Fiscal Year 2018	Dogs held by facility but not used (USDA column B)	Dogs used in research; no pain and no pain medications (USDA column C)	Dogs used in research; pain involved and pain drugs used (USDA column D)	Dogs used in research; pain involved with no pain medication (USDA column E)	TOTAL number used (columns C+D+E) (USDA column F)
Total reported by USDA-APHIS <sup>a</sup>	6,366	41,092	17,888	332	59,312
Total reported in 2018 Annual Report Animal Usage by Fiscal Year Report <sup>b</sup>	6,387	41,317	17,752	332	59,401

<sup>a</sup> Data obtained directly from USDA through a FOIA request; this information also provided details on the number of dogs used per pain category for each of the 328 institutions reporting the use of dogs in FY2018. <sup>b</sup> Data reported on USDA-APHIS website<sup>6</sup>.

accounted for in 2018 research publications, indicates that the number of dogs reported in research publications underestimates the total number of dogs used annually by US institutions.

“Beagle” was the most common dog breed used in research, reported in 27 of the 97 publications (28%) and in 33 of the 118 grants (28%), resulting in the use of more than 795 and 1,790 beagles, respectively (Tab. 1). Beagles were also often used in combination with other breeds, and three grants and three publications that used only beagles did not provide the number of dogs used, so beagles were used to an even greater extent than identified by these numbers.

The second most common breed to be used was “mongrel and/or a mix of breeds,” identified in 23 publications (> 327 dogs) and 19 grants (> 1,205 dogs). “Hound or hound mix with or without other breeds” was the third most common breed identified in the publications and grants.

Dog breed is a type of basic information needed to identify the experimental animal and is part of the animal use reporting requirements for scientific publications in adhering to the ARRIVE Guidelines<sup>8</sup>. Two publications and 10 grants did not provide the number of dogs or the dog breed, and 20 additional publications and 30 grants did not identify the breed of dogs used for research. Missing animal use information in the grants may be due to redaction.

### 3.3 Biomedical research categories and subcategories of dog use

The purpose of each study involving the use of dogs was identified by categorizing the research in each grant or publication using a standard biomedical nomenclature. As explained in the Methods section, a simplified version of the “research categories” and “research subcategories” used in the annual reporting of animal use in the EU was adopted for this study (EC, 2012). The types of biomedical research involving the use of dogs, indexed according to “research category” and “research subcategory” for 97 research articles and 118 grants, are summarized in Figure 1 and Figure 2, respectively. The corresponding numerical data are provided in Table S2<sup>17</sup>.

The most common “research category” for publications and

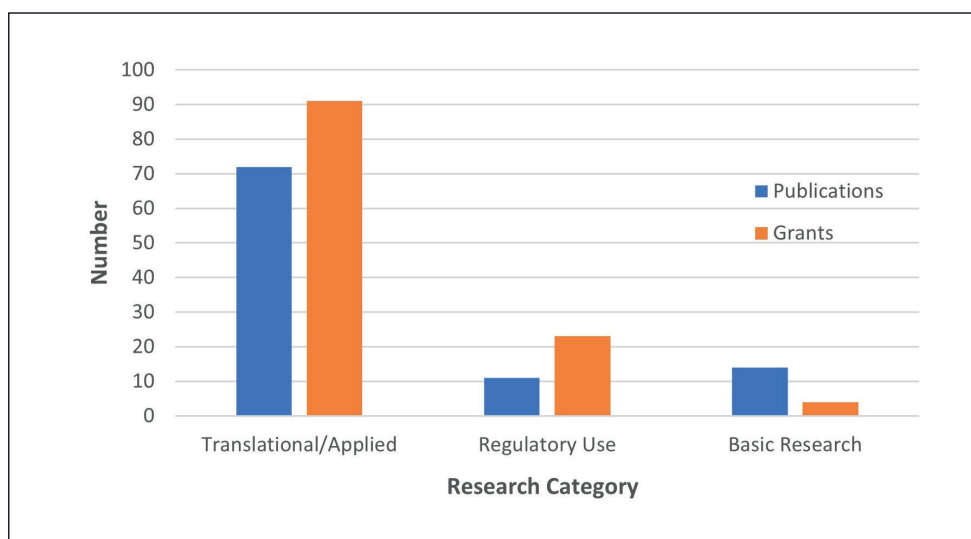
grants was “translational/applied research studies,” applicable to 72/97 research articles (74%) and 91/118 grants (77%) (Fig. 1). Fourteen articles (14%) and four grants (3%) could be categorized as “basic research studies,” and 11 articles (11%) and 23 grants (19%) involved studies for “regulatory use.”

The type of research in each publication and grant was further categorized into one of 12 “research subcategories” (Fig. 2). “Cardiovascular disorders” was the most common subcategory, accounting for 32/97 (33%) of the publications and 23/118 grants (19%), most of these belonging to the “translational/applied” research category, 25/32 and 19/23, respectively. The second most common “research subcategory” for the publications was “cancer” (16/97), often involving studies for therapeutic development; for grants it was “other disorders” (16/118), closely followed by “cancer” and “nervous and mental disorders.” The relatively large number of grants in the “other disorders” subcategory is due to grants related to dental, hematology, and vocal cord studies. “Musculoskeletal disorders” was another common type of research using a dog model.

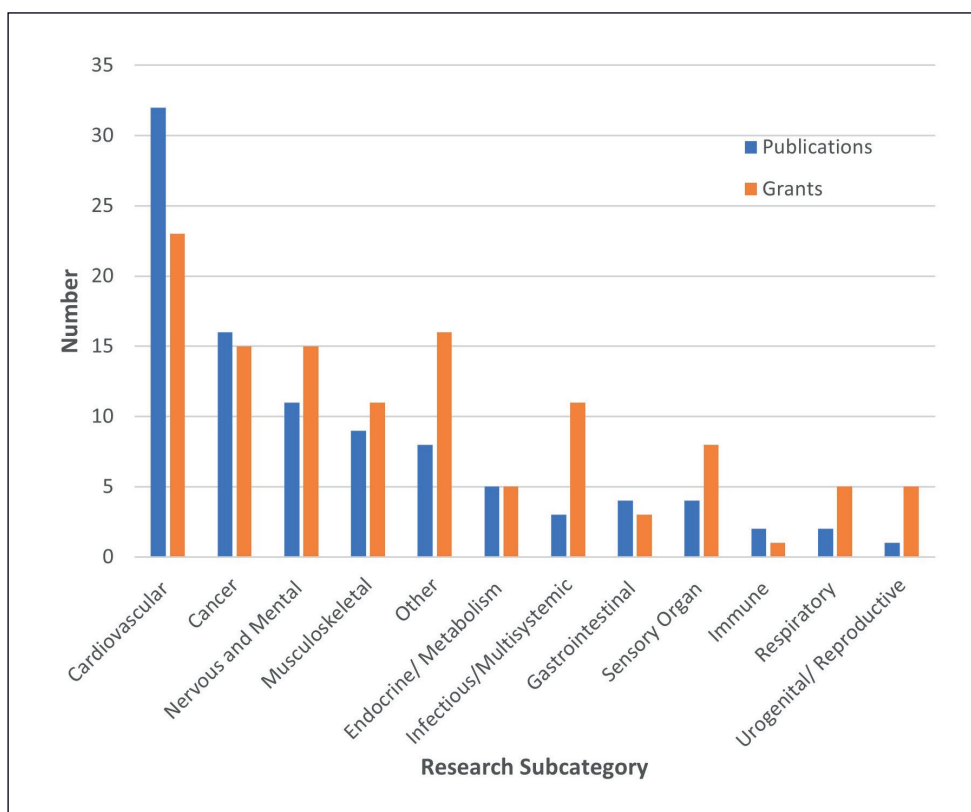
Various limitations were encountered in assigning a “research category” and “research subcategory” to each publication and grant. Some articles and grants did not sufficiently or clearly explain how the study data would be used, or the language used was ambiguous. Most of the grants described research to be conducted over multiple years and included aspirational statements about future clinical relevance and/or regulatory submissions. Other limitations regarding the grant data, as mentioned previously, were NIH limits on the grants provided and their redaction process.

In the EU nomenclature, “non-regulatory toxicology” is a separate “research subcategory,” but for this study “non-regulatory toxicology” could often not be clearly distinguished from “translational/applied research” and/or from “regulatory use.” Many of the “translational/applied research studies” for both grants and publications appeared to be “non-regulatory toxicology,” so it was more useful for the purpose of this study to focus on identifying the biomedical type of research.

Grants and publications reporting studies that appeared to be generating data for use in regulatory submissions were identi-



**Fig. 1: Classification of the 97 publications and 118 grants in the study dataset according to “research category”**  
Numerical data are provided in Table S2<sup>17</sup>.



**Fig. 2: Classification of the 97 publications and 118 grants in the study dataset according to “research subcategory”**  
Numerical data are provided in Table S2<sup>17</sup>.

fied as “regulatory use.” The attempt was made to exclude studies with only aspirational statements about regulatory applications, but category decisions without the original author’s input must be considered as third-party interpretations of the study’s intent. For EU animal use reporting, “regulatory use” is assigned a toxicological test subcategory. The grants and publications differ from EU reporting in that they cover multiple experiments/procedures, so one type of toxicological test cannot be assigned.

Therefore, the 12 biomedical “research subcategories” were also used to subcategorize grants and publications categorized as “regulatory use.”

“Animal use and disorders” is another “research subcategory” in the EU nomenclature that was used differently here. One of the data types collected for each grant and publication was “species to benefit” using the categories of human, dog, or both. None of the grants were found to benefit only dogs, probably due to the



**Tab. 3: Species justifications provided for the use of dog as the experimental model in 97 research publications and 118 grants**  
Each publication identified from zero to four different justifications and each grant from zero to seven justifications.

Species justification	Number of publications	Number of grants
Animal model needed for preclinical studies	21	66
Size – large animal model needed	15	57
Disease phenotype similar in dogs and humans	19	39
Anatomically/physiologically similar to humans	11	37
Historical dog data available	2	48
Naturally occurring disease/condition in dogs	21	25
Use of alternatives not possible	2	50
Dogs are outbred model	0	5
Good model for repeated studies	0	7
Long life span	1	4
Docility of dogs	1	4
Dog model to study dog disorder <sup>a</sup>	12	0
<b>Not provided or unclear</b>	<b>30 (31%)</b>	<b>4 (3%)</b>
Average number of justifications per article or grant	1.4	2.9

<sup>a</sup> This particular justification, relevant only when the “species to benefit” was dogs, is the only one listed that may not have been explicitly stated in the publications. There were no grants benefitting only dogs.

NIH selection process. Fourteen of the published studies were identified as benefitting dogs. Rather than placing these in one “animal use and disorders” subcategory, these studies were also subcategorized according to their biomedical type. Table S2<sup>17</sup> includes the numerical breakdowns of the species to benefit in each subcategory (numbers in parentheses – see Tab. S2<sup>17</sup> footnote).

### 3.4 Reporting of species justification

The 97 publications and 118 grants were reviewed to determine the primary justifications researchers provided for using dog as the experimental animal (Tab. 3). Species justifications were categorized according to the justification(s) stated by the author(s). Some studies provided multiple justifications, and some provided none. On average, more justifications for the use of dogs were provided in the grants than in the research articles.

Almost a third of the research publications, 30/97 (31%), did not provide a clearly stated justification for using dog as the experimental animal. On the other hand, only 4/118 grants were missing a species justification, and these missing justifications may have been located in redacted sections because NIH grant guidance requires this information<sup>15</sup>.

The most common species justification provided in the publications and grants was “animal model needed for preclinical studies,” which corresponds to the majority of grants and publications involving some type of translational/applied research (the category that includes non-regulatory toxicology) or “regulatory use” (Fig. 1). Other common species justifications used in both the publications and grants were: “naturally occurring dis-

ease/condition in dogs,” “disease phenotype similar in dogs and humans,” “size – large animal model needed,” and “anatomically/physiologically similar to humans.” Two justifications commonly found in the grants, but not in the publications, were “use of alternatives not possible” and “historical dog data available.” NIH grant applicants are required to “*explain why the research goals cannot be accomplished using an alternative model*”<sup>15</sup>, which probably accounts for their claim that alternatives are not available. The absence of any discussion or consideration of alternative research models was notable in the majority of the research publications.

### 3.5 Reporting of pain management

The research publications were assessed for whether an explanation of pain management for the experimental dogs was reported within the publication (Tab. 4). As noted in the Methods, pain management is a complex topic, and an analysis of the processes, therapeutics, and whether they were adequate is beyond the scope of this study. What is explained here is whether or not pain management was reported, which is an essential type of animal use information required in journals adhering to the ARRIVE Guidelines<sup>8</sup>. This type of assessment was not applicable to the grants because NIH grant applications are required to include detailed reporting on pain management as part of the “Minimization of Pain and Distress” subsection of the Vertebrate Animal Section (VAS). Grant reviewers are instructed to rate an application “*unacceptable if all required items [in the VAS] are not addressed adequately or found inappropriate*”<sup>15</sup>, and NIH staff also



**Tab. 4: Research publications reporting, or lacking reporting, on pain management<sup>a</sup>**

Description of pain management was...	Number and percent of publications	Number of dogs
Not needed	34 (35%)	> 416
Clear	6 (6%)	≥ 399
Vague/incomplete	<b>6 (6%)</b>	<b>352</b>
Missing	<b>51 (53%)</b>	<b>&gt; 790</b>
Total	97 (100%)	> 1,957

<sup>a</sup> Detailed information on pain management is already a required part of NIH grant proposals<sup>15</sup>.

confirm that all VAS criteria are addressed.

There was a clear distinction in the effort made to explain pain management among the publications when it was reported. Publications that made an effort to provide a clear/useful explanation of pain management were categorized as “clear.” Studies where pain management reporting was categorized as “not needed” include those using *ex vivo* dog tissues and studies using procedures where dogs were euthanized at the end of a surgery. Publications where pain management reporting was minimal are categorized as “vague/incomplete.” An example of “vague or incomplete” would be the reporting of anesthesia use during a survival surgery with no explanation of pain management following the surgery (Yoo et al., 2018, p. 13 Suppl. data). The reporting of pain management for drug infusion studies to evaluate pharmacokinetics and toxicity was also categorized as “vague/incomplete” when there was insufficient information to know pain management was “not needed.” Publications reporting nothing about pain management when the need was expected due to the described procedures are categorized as “missing.”

The categories used here are intended to explain only the “reporting of pain management” and make no judgment on whether the pain management described in a publication was correct or sufficient. Information related to animal care and pain management was often located in different paragraphs and even different sections of a publication. Overall, the degree of reporting of pain management in publications varied substantially and was much less comprehensive than what is reported in the VAS of NIH grant applications<sup>15</sup>.

An explanation for pain management for the dogs used in experimental procedures was “missing” or “vague/incomplete” in 57/97 (59%) of the publications (Tab. 4). That means anyone reading the publication would not know if pain was treated, if it was adequately treated, how it was treated, or if the pain or pain treatment might impact the experimental outcome. Even when needed, such as following a survival surgery, an explanation for the management of pain was often missing. A total of more than 1,142 dogs were reported as used in the 57 publications with “vague/incomplete” or “missing” explanations for pain management. Pain management was found to be clearly described in only six (6%) of the publications and “not needed” in 35%, representing about 42% of the dogs used in procedures expected to require pain management.

A second type of information used to assess the extent of painful experimental procedures experienced by dogs used in research by US institutions was obtained through direct data requests submitted to the USDA. USDA-APHIS statistics for FY2018, shown in Table 2, indicate 332 dogs were used that year in painful procedures without the use of pain medication. The information provided by USDA-APHIS also identifies the 328 US institutions reporting the use of dogs in FY2018. Out of the 328 institutions, 16 institutions were involved in using the 332 dogs in painful procedures without the use of pain medications.

### 3.6 Reporting on source of dogs

The most common source of dogs used in the studies reviewed here was “commercial breeders,” the source in 21% of the publi-

**Tab. 5: Source of dogs used in the experimental procedures of 97 publications and 118 grants**

Dog source	Number of publications	Number of grants <sup>a</sup>
Commercial breeders	20 (21%)	68 (58%)
Other breeding colony	10	19
Client-owned (pets)	10	10
Client-owned and other	6	3
Breeder and/or other breeding colony	1	4
Breeder and primary cells or tissues from commercial supplier	2	0
Dog primary cells or tissues	9	0
<b>Source not provided</b>	<b>39 (40%)</b>	<b>14 (12%)</b>
Total	97	118

<sup>a</sup> Grants were selectively provided and redacted by NIH, so grant data may not represent the exact distribution.

**Tab. 6: Fate of dogs at study termination identified in 97 research articles and 118 grants**

Dog endpoint	Number of publications	Number of grants <sup>a</sup>
Euthanize	51 (53%)	61 (52%)
Euthanize and death from procedure	2	0
Reuse (usually dog colony dogs)	3	1
Re-home (return to owner) <sup>b</sup>	12	2
Adoption	1	1
Remain under lab observation; euthanize if necessary	4	1
Mixture of endpoints <sup>c</sup>	3	36
<b>Not reported</b>	<b>21 (22%)</b>	<b>16 (14%)</b>
<b>Total</b>	<b>97</b>	<b>118</b>

<sup>a</sup> Grants were selectively provided and redacted by NIH, so grant data may not represent the exact distribution. <sup>b</sup> Usually also stating “euthanize if necessary.” <sup>c</sup> Usually including “euthanasia” or “euthanize if necessary.”

cations and 58% of the grants (Tab. 5). A large proportion of the publications and grants, however, did not identify a dog source: 40% and 12%, respectively. Therefore, commercial breeder-procured dogs may have been an even larger source than indicated by the data. The source for dogs is a required type of content in the Vertebrate Animal Section of NIH grant applications<sup>15</sup>. Therefore, when missing, the dog source is assumed to have been redacted.

“Other breeding colonies,” such as those owned by universities or companies breeding dogs for their own research, was the second largest source of research dogs. Client-owned dogs was the third most common source, and these were typically dog patients enrolled in a veterinary study or clinical trial. To be included as relevant based on the criteria for this study, a clinical study had to be experimental rather than just therapeutic.

Dogs, dog procedures, and/or dog tissues were reported as procured from foreign countries in at least 11 of the 97 research publications. This is not surprising because research articles often have many co-authors, and articles with non-US co-authors could still meet the criteria for inclusion in this study. Since 40% of the research publications did not report their source for dogs, it is unknown whether all dog procedures conducted in other countries are identified. Other countries conducting experimental procedures on dogs or providing dogs or dog tissue included Canada, China, France, South Korea, United Kingdom, and Poland. Foreign dog sources and experimental procedures were not identified in the grants.

### 3.7 Reporting on fate of dogs

The fates of dogs at the end of the research studies are summarized in Table 6. Euthanasia was the endpoint for the dogs used in a majority of experimental procedures, reported in 53% of the publications and 52% of the grants. Euthanasia was also combined with other endpoints in some studies, indicating its even wider use. “Reuse” could be assumed for uninjured dog colony

dogs, but when not specified was classified as “not reported.” The “re-home” category refers to pet dogs that remained with or were returned to their owners following the study. An example of a mixture of endpoints would be “re-home and euthanize,” where client-owned dogs were returned to their owners and purpose-bred beagles were euthanized. Two publications and five grants mentioned the highly preferred fate for dogs of “adoption” (some under “mixture of endpoints” in Tab. 6).

Like the other types of information on dogs used for research, a substantial number of grants and publications did not explain what happened to the dogs at the end of the study. Twenty-two percent of the publications and 14% of the grants did not specify the fate of the dogs. Grant applications are required only to provide the “method of euthanasia,” so other dog fates may be missing in grants in addition to possibly being redacted.

## 4 Discussion

Information on the purpose of laboratory animal use is an essential statistic for understanding trends in animal use and for identifying research areas that should be prioritized for the development of alternatives. The initial purpose of this study was to identify the types of biomedical research being conducted in US laboratories that use dogs as the experimental animal as well as the types of research using the most dogs, because this information is not a part of the required information on animal use reported annually by US institutions to USDA-APHIS.

Many issues were uncovered in this examination of recent, well-defined sets of grants and publications reporting the use of dogs in biomedical research by US institutions. Findings from this study that will be discussed further include: (1) the use of an ontology to categorize the biomedical types of research using dogs, (2) the types of biomedical research found to use the most dogs, (3) the inability to identify the type/purpose of research for

all dogs used by US institutions because (a) this information is not a part of required animal use data reported to USDA-APHIS and (b) the majority of dogs used for research purposes are not reported in scientific publications, (4) the substantial number of scientific publications missing some of the basic information typically reported for an animal model, and (5) similar trends seen in the grants and the publications for commonly reported types of animal use information.

#### 4.1 Ontology to categorize biomedical research uses of dogs

Before any data could be collected, a nomenclature or ontology to categorize the type/purpose of biomedical research involving the use of dogs had to be identified. A subset of the nomenclature used by the European Commission for reporting the research purpose of animal use as part of its annual animal use reporting requirements was adopted as the most useful and relevant for this study (EC, 2012). Three “research categories” and 12 “research subcategories,” identified in Table S1<sup>17</sup>, were determined as a useful system to assign the research purpose for dogs used in studies described in the grants and publications. Three additional types of research that commonly involved the use of dogs, dental, hematology, and vocal cord studies, had to be categorized as “other disorders,” and these should be considered as additional subcategories in future studies needing a similar ontology. Moving forward, it could benefit researchers conducting studies on the laboratory use of dogs to have a standardized and internationally accepted nomenclature/ontology.

#### 4.2 Types of research using the most dogs

Identifying the types of research and/or testing involving the largest number of animals is a benchmark sometimes used to prioritize the allocation of resources for the development of alternative research models/methods. Dogs were found to be used most often in translational/applied types of research in the publications and grants examined for this study (74% and 77%, respectively), which includes “non-regulatory toxicology” studies. Studies developing data for regulatory use were a little less common in publications than grants (11% and 19%, respectively), which might be because not all of the funded studies developing data to support regulatory submissions are published, but is more likely due in this study to the aspirational product development language and wider array of experiments covered in many of the grant applications leading to some uncertainty in assigning the translational versus regulatory use category. Other limitations in assigning “research category” to the publications and grants are explained in the Methods section.

Overall, a large portion of the research conducted using dogs in the examined grants and publications was conducted for the purpose of product or procedure development, either supporting or anticipating support for a regulatory submission. Four of the most common species justifications identified in the publications and grants, “animal model needed for preclinical studies,” “size – large animal model needed,” “disease phenotype similar in dogs and humans,” and “anatomically/physiologically similar

to humans” (Tab. 3) also suggest the intended use of the dog data was to support a current or anticipated regulatory application. The NASEM panel assembled to investigate dog use at the Department of Veterans Affairs procured USDA-APHIS dog data for FY2017 and found that out of 60,190 dogs used by US institutions more than half (34,875 or 58%) were used by private research organizations or industry, which they assumed as primarily for research, product development, and testing for regulatory submissions (NASEM, 2020, p. 146). The most recent report of statistical data on the use of animals for scientific purposes by EU Member States, for the years 2015-2017, showed a similar finding in reporting that almost half of the dog use was for “regulatory use” studies (EC, 2020a, Figure 2.3).

“Cardiovascular disorders” was the most common “research subcategory” involving the use of dogs in the publications and the grants (33% and 19%, respectively), most often as a translational/applied research study. The NASEM panel report, likewise, found the most common research using dogs involved some type of cardiovascular procedure (NASEM, 2020). A justification often given for using dogs in cardiovascular research is the need for a large animal model. Oh and Ishikawa (2018) report the advantages of large animal models to be “*the similarities in size, anatomy, and physiology to the human heart*.” On the other hand, large animal models for cardiovascular disease do not replicate the obesity, metabolic disease, and aging most often involved in human disease (Oh and Ishikawa, 2018), and for some types of cardiovascular studies the mechanistic responses of the dog cardiac model differ from the human (Shen et al., 2017). For example, animal models for cardiac arrhythmias have been unsatisfactory because there are multiple causal factors that are not fully understood, and human genetics may be a contributing factor (Milan and MacRae, 2005), but random source dogs have sometimes been found to be useful arrhythmia models (NRC, 2009a). While there are many challenges for replacing dogs in cardiovascular research, there is also the opportunity to gain more predictive human models.

A number of *in silico*, *in vitro*, and *ex vivo* models have been developed for cardiovascular research (Ishikawa, 2018; NASEM, 2020; Savoji et al., 2019). Dogs may be sacrificed for cardiac cells and tissue that are used *ex vivo* to conduct mechanistic studies, so having well-established *in vitro* models has the potential to reduce some dog use, and *in silico* models are being evaluated as alternatives for electrophysiology studies. Cardiomyocytes derived from human induced pluripotent stem cells (hiPSCs) are being used to detect cardiotoxic drugs and to develop various cardiovascular models (Funakoshi and Yoshida, 2021; Maddah et al., 2020; Ribeiro et al., 2019). *Ex vivo* tissue models offer more research options but are often procured from animals. Human engineered cardiac tissue is a promising emerging technology with the potential to replace some animal use in cardiovascular research while overcoming issues with extrapolating data between species (Cashman et al., 2016; Gähwiler et al., 2021; Li et al., 2018; Simon and Masters, 2020; Turnbull et al., 2014, 2018). Several approaches using donated human hearts unsuitable for transplantation have also been developed as research models (NASEM, 2020).



### 4.3 Number of dogs used for research in the United States

USDA-APHIS does not require reporting on the purpose for animal use, so the number of dogs used for different types of biomedical research and for regulatory testing in the US is not known. The use of almost 60,000 dogs per year for research by US institutions has been reported to USDA-APHIS every year for the past several decades<sup>6</sup>, for example, the 59,312 dogs reported for FY2018 (Tab. 2). The results of this study found research reported in scientific publications in 2018 to account for around 8,000 dogs used by US institutions (see Section 3.2), leaving approximately 50,000 dogs to be accounted for in 2018. Some of this discrepancy may be explained by the inclusion criteria used for this study, which limited the studies to those involving invasive procedures using dogs. Additionally, the use of dogs in academia for medical, dental, and veterinary education and training purposes would not be reported in research publications. Researchers tracking approved animal studies in the Netherlands found that only 26% of research animals ended up being reported in scientific publications (van der Naald et al., 2020). The purpose of that study was to evaluate possible reasons such as publication bias or selective publication of preclinical animal studies, and similar reasons could account for part of the difference in the number of dogs reported to USDA-APHIS and the lower number found in research publications. Research using certain species, like dogs, is considered a sensitive topic, which may impact publication decisions by some organizations. Considering the NASEM finding that more than half of the dogs reported to USDA-APHIS in FY2017 were used by private research organizations or industry (NASEM, 2020, p.146), along with the finding of this study that the majority of dog use in grants and publications is for translational or regulatory use studies, suggests the largest reason for not all dogs being accounted for in publications is their use for product development and regulatory testing in research that remains unpublished.

### 4.4 Incomplete/missing dog data in publications: Number, breed, source, fate, species justification, and pain management

An unexpected finding from this study was the amount of missing or incomplete information on the research animal, i.e., dogs, in some of the publications. Details on the animal model and use of animals are generally accepted as essential to providing a complete description of the research methods<sup>8</sup> (NIH OLAW, 2015; NRC, 2011). Variables such as age, breed, sex, and source of experimental animals, as well as pain management procedures, may impact the data and thus the study results and reproducibility (Fleischer et al., 2008; Hanton and Rabemampianina, 2006; Harper et al., 2003; NRC, 2009a,b). For this study, defined sets of grants and publications were assessed for dog number, breed, source, species justification, and fate (Tab. 1, 3, 5, 6), and publications were assessed for their reporting of pain management procedures (Tab. 4). The ARRIVE guidelines, developed

to guide best practices for scientific journals in reporting animal use, specify the inclusion of the types of information identified as missing or incomplete in the publications accessed for this study<sup>8</sup>. ARRIVE requires the reporting of even more types of animal use information and provides “a checklist of information to include in publications describing animal research”<sup>9</sup> (Percie du Sert et al., 2020b). However, the adoption of the ARRIVE guidelines on animal use reporting by journals is voluntary, and other animal use regulations and guidance do not provide specific requirements on animal use reporting in scientific publications. On the other hand, federally-funded grants such as the NIH grants accessed for this study require detailed reporting on animal use (NIH OLAW, 2015;<sup>15</sup>), so when any of the animal use data was missing from grants accessed for this study it was assumed this was due to the NIH redaction process.

Species justification is important because it explains the potential for an animal model to provide results relevant to humans. Thirty-one percent (31%) of the publications did not provide a clearly stated justification for the selection of dog as the experimental model (Tab. 3). On the other hand, species justification, part of the information required for NIH grant applications,<sup>15</sup> was rarely missing in the grants (so not selected for redaction). NIH grant applicants are also required to explain whether alternatives to animals are available, thus explaining the large number of grants with the justification “use of alternatives not possible.” Unfortunately, the research publications rarely mentioned any consideration of alternative methods or models. The panel that drafted the NASEM report examining dog use in VA research took issue with some of the species justifications identified by researchers. The report noted, “*Principal investigators frequently cited previous experience with and historical data in dog models as primary justifications for using laboratory dogs. These justifications are insufficient alone and constitute a form of circular reasoning that perpetuates the use of laboratory dogs without adequate examination of alternatives*” (NASEM, 2020). Around 40% of the grants examined for this study also claimed the justification of “historical dog data available,” but it was cited in only two of the research publications. This justification does, however, appear to be an “implied justification” for the many “cardiovascular disorders” studies that did not provide a justification for their selection of a dog model.

The source of the dogs used for research was most often a commercial breeder or private breeding colony; however, 40% of the publications and 12% of the grants did not provide a dog source (Tab. 5). The source for dogs used in NIH grant proposals is required information, so grants missing this information would have had it redacted<sup>15</sup>. When the source of dogs is not provided, there is uncertainty about the reliability of the study results. For example, dogs from random sources such as pounds or class B dealers have an unknown medical history and, therefore, are not reliable models for some types of research. For example, differences in some types of cardiovascular responses have been reported for random source versus pure-bred dogs (NRC, 2009a). NIH addressed this issue in 2013 when it determined it would no



longer permit NIH funding to be used for the purchase of random source dogs<sup>18</sup>. Two additional observations related to missing information on the source of dogs were made during the course of this study. The first was the purchase and use of dogs in foreign countries for US-funded studies, which is covered in the Results section. Second, a number of noncommercial dog colonies were described as the source of dogs in grants and publications, with some dog colonies being supported by NIH grants and some breeding new genetic lines of dogs. The high cost of dogs has been one of the major factors limiting the number of dogs used for research. As research dogs become more available, possibly through foreign sources and noncommercial breeders, the cost, which has served to limit some dog use, may decline. This could have a negative impact on 3Rs initiatives.

The fate of dogs at the end of a study was missing in 22% of the publications and 14% of the grants (Tab. 6). Research animal fate, except for the method of euthanasia, is the only animal use data examined in this study that is not specifically required to be reported in NIH grant proposals<sup>15</sup>. The fate of the dogs is not expected to impact the research results; however, not providing this information does affect animal welfare concerns such as whether animals are being reused and whether surviving animals are being made available for adoption. Some universities and US agencies now make surviving research animals available for adoption<sup>19,20</sup>, so when the fate of research dogs is not provided the adoption opportunity may go unrecognized. NIH provides guidance for institutions that want to implement a research animal adoption program, including the informational webinar “The 4<sup>th</sup> R: Rehoming, Retirement and Release” to assist with this process<sup>21</sup>. Regarding the topic of reusing research animals, EU reporting now requires information on animal reuse due to its potential impact on animal welfare (EC, 2020a,b).

The most concerning lack of information regarding dogs used in research, however, was the missing or insufficient information in the research publications on the management of pain following experimental procedures using dogs. US and EU governments as well as animal welfare organizations all recognize the importance of preventing and reporting on pain experienced by animals used for research. The importance of providing adequate methods to prevent, when possible, and alleviate, when needed, pain and distress in laboratory animals has been recognized in federal legislation and guidance for many decades (NIH OLAW, 2015; NRC, 1994, 2009b, 2011), and detailed explanations for pain management are required in the Vertebrate Animal Section of NIH grant proposals<sup>15</sup>. EU requirements for reporting animal pain were strengthened recently with a new requirement for reporting on the actual severity of pain experienced by animals from experimental procedures. The rationale is that

this “allows focusing efforts, not only on areas with the highest numbers of animal uses, but also on those with most severe impact on animals” so that efforts can be made to refine these uses (EC, 2020a). And the reporting in publications of procedures to manage research animal pain is required when following the ARRIVE guidelines<sup>8</sup>. The international working group updating the ARRIVE guidelines explained that “A thorough description of the procedures used to alleviate pain, suffering, and distress provides practical information for researchers to replicate the method” (Percie du Sert et al., 2020a). The examples provided on the ARRIVE website at this time are primarily related to surgical pain management, but some non-surgical procedures may also need pain management consideration.

The finding of pain management procedures to be missing or minimally explained in 59% of the publications examined in this study, involving the use of more than 1,142 dogs (Tab. 4), is notable. Incomplete or missing information on whether and how animal pain is managed in a research study can have profound implications for both animal welfare and experimental outcomes. The presence of pain or the use of an unexplained medication for pain each have the potential to affect study results and, therefore, the ability to reproduce the results (Carbone and Austin, 2016; Fenwick et al., 2014; Guittin and Decelle, 2002; NRC, 2009b). The withholding of analgesia has been described as appropriate in only several situations, such as when it would or could interfere with the study results, or when pain/pain control itself is being studied (Fenwick et al., 2014), and these should be explained in a publication when relevant. Previous studies have also identified insufficient reporting on pain management procedures in scientific publications (Bertrand et al., 2018; Carbone and Austin, 2016; Coulter et al., 2009; Uhlig et al., 2015). Bertrand et al. (2018) found only 49.9% of 397 publications using non-human primates in surgical procedures reported an anesthetic regimen. Carbone and Austin (2016) examined 400 research publications involving survival surgeries across various species and found only 338/400 to include “any mention of use of anesthetics or analgesics,” and 240 of those 338 did not mention post-surgical analgesia. Carbone and Austin (2016) made the astute observation that “animal welfare regulations do not include guidance on publishing animal data, even though publication is an integral part of the cycle of research and can affect the welfare of animals in studies building on published work.”

Thus, an important finding from this study is the continued inadequate information provided on the experimental animal, dogs in particular for this study, when their use is reported in scientific publications. The ARRIVE guidelines, like NIH grant policy, already specify that all of the types of animal use information identified as missing or incomplete in this study be reported in pub-

<sup>18</sup> NIH (2013). Notice regarding NIH plan to transition from use of USDA Class B dogs to other legal sources. <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-034.html>

<sup>19</sup> Bucchino, R. (2020). New FDA policy allows lab animals to be adopted after experiments. Thehill.com. <https://thehill.com/policy/healthcare/482074-new-fda-policy-allows-lab-animals-to-be-adopted-after-experiments>

<sup>20</sup> Johns Hopkins Medicine. Adopting animal companions. <https://www.hopkinsmedicine.org/research/resources/offices-policies/animal-care/adopting-animal-companions.html>

<sup>21</sup> <https://olaw.nih.gov/education/educational-resources/webinar-2019-06-13.htm>





lications and grant proposals, respectively<sup>8,15</sup>. However, the voluntary ARRIVE guidance appears to need broader adoption by journals to ensure more complete reporting on animal use. Information on the ARRIVE website explains how funding and other organizations, in addition to journals, can become involved in promoting better animal use reporting<sup>22</sup>.

When publications provide incomplete information on the animal model, it can result in findings that cannot be reproduced and, therefore, do not meet NIH guidance on reproducibility<sup>23</sup>. Therefore, it would make sense for NIH grant policy to address animal reporting requirements when NIH-funded studies are published. In fact, the importance of “methods/methodological reproducibility” is one of the elements addressed in a recent NIH Report<sup>24</sup>. Addressing reproducibility issues alone will not reduce the use of dogs in research, but this knowledge adds to the uncertainty of the relevance of the dog model in preclinical studies where dogs are commonly used, leading to the questions of: (1) whether dog data have been as essential to preclinical studies as claimed, and (2) how much the dog data may be contributing to post-market drug failures and product toxicities. For example, Kringe et al. (2020) conducted a systematic review of research using large animal models for stroke research and found that, although they are “believed to offer significant benefits for translational stroke research,” the methodological quality was mediocre due to deficiencies in “reporting study subject details and welfare.”

## 5 Conclusions

Considering the NASEM panel’s assessment of VA research using dogs, which concluded that some experiments conducted on dogs were unnecessary and that certain types of research should not be conducted using dogs (NASEM, 2020), the justification(s) for using a dog model for any experimental procedure should continue to be scrutinized. As noted, the “responsibility lies with the principal investigator, scientific review committee, and institutional animal care and use committee to know the literature and accurately determine whether the laboratory dog is still the best model for any particular study” (NASEM, 2020, p.4).

This study began with the simple goal to identify the types of biomedical research using dogs and the types of research using the most dogs, and many additional topics have been identified that could benefit from further study. It was interesting, also, to observe the similar trends in US dog use statistics found between the grants, the publications, and the NASEM report (NASEM, 2020), considering these are independent datasets. The research type/purpose for the majority of dogs used by US institutions, however, remains uncertain due to the lack of required reporting of this data in the US.

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#### Data availability statement

The research data are available upon request from the corresponding author to researchers planning to use the data for additional research purposes. Institutional verification of planned research may be requested.

#### Conflict of interest

The authors declare they have no financial conflicts of interest.

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