

VA Response
to Follow-up Questions of the Committee for the
Assessment of the Care and Use of Dogs in Biomedical Research Funded by or Conducted at
the US Department of Veterans Affairs
Submitted 2/22/19

The key to understanding the relationships among the pieces of information in the various lists of VA research with dogs that we have provided to the committee, is to keep in mind that all of the information reflects the multi-modal, collaborative, and incremental nature of rigorous biomedical research. The analogy of a jigsaw puzzle was described in the VA presentation for Meeting #1, for thinking about this process: VA research is like the process of assembling a very large jigsaw puzzle, with many people working individually or as teams, each choosing a different portion of the puzzle to work on, each building on and contributing to the work of the others. All of the efforts are valuable even if some only identify where pieces don't fit. All of the pieces that do fit are essential to the final product, even though only one person gets to put in the final piece that makes the picture (or some portion of it) complete.

The puzzle that VA research is focused on is that of how to restore/improve the health and well-being of Veterans. Different investigators work on different pieces of this puzzle (some on restoring the function of respiratory muscles of individuals with spinal cord injury, and others on addressing problems associated with cardiac electrophysiology, for example), but all depend on earlier work that they themselves and others have done, and all contribute to future work that they themselves and others will do (with some of the work supported by VA and some not, some of the work with dogs and some not).

We have provided several different collections of information about VA research with dogs to the committee, each focused to address specific questions that we anticipated would be of interest to the committee, or questions that the committee asked. The collections provided so far are as follows:

- Currently active VA research with dogs (Appendix 8) – These describe the portions of the puzzle that VA research with dogs currently is addressing. Because this research is currently in progress, and the results are not yet known, there are no publications yet describing the results.

There are numerous publications of earlier research, often by the same investigators, involving similar models and procedures, but also many by other investigators using other models and procedures, which were responsible for fitting in other pieces of the puzzle to which the current work is designed to contribute. It is not possible to provide comprehensive lists of these publications, as each publication reports the results of work stimulated by, and critically dependent on, the results of work done and published earlier. This means that each research effort currently underway is related to a large network of publications in the literature that does not have discreet boundaries. Some of the more recent publications of research that is

relatively closely related to the specific currently active VA research with dogs are provided in the attached list, “Publications Related to Appendix 8”.

When we refer to “currently active” or “currently in progress” research with dogs, we mean work for which there is an IACUC-approved protocol currently in place for procedures to be conducted with dogs, and for which the work with dogs is currently being conducted. The “protocol” describes the specific procedures to be performed with dogs, why they are necessary, and how the welfare of the dogs is safeguarded. The protocol is one component of the overall research “project”, which is designed to address a specific research question and may require integration of data gathered in many different ways. A project may include more than one animal research protocol, and more than one species of research subject, as well as a wide variety of rigorous laboratory, analytical, and statistical analyses. Typically, in research with animals, the work described in the “protocol” is only the beginning of the effort. After that, there is significant amount of further work to be done – processing and analysis of tissues samples, analysis of observations made during the approved procedures with the animals, integration of observations made during the approved animal procedures with the results of analyses that could only be completed afterward, interpreting the integrated data. Some of this may begin while work with the animals is still in progress, but there is most often much left to do after the work described in the approved “protocol” is complete, continuing until well after the IACUC-approved protocol expires. At that point, the “research with dogs” would be considered “inactive” for the purposes of Appendix 8, but work on the “project” overall would still be in full swing. Responsible researchers make every effort to squeeze every last bit of useful information out of the observations and data collected from procedures conducted with animals, which are designed to maximize useful information from each animal. For research with dogs, because of the complexity of the work, it would not be at all surprising for the subsequent work on the project to take a year or two of focused effort, before a paper could even be drafted and submitted to a peer-reviewed journal. The peer-review and revision process can easily take additional months, so it is unremarkable for it to take few years after the end of “active research with dogs” before the results are formally published.

- Examples of historical accomplishments with recognized clinical benefits of VA research with dogs (Appendix 6), including a representative peer-reviewed publication for each – These are just a sampling of VA research with dogs that has led to easily recognized healthcare advances. There is no expectation that this is a comprehensive listing of recognized accomplishments. There is also certainly VA research with dogs that has been published, for which we will only understand sometime in the future, how it contributes to recognized healthcare advances that have yet to be made (work that has put in pieces of the puzzle in areas where the picture is still quite unclear). The publication provided for each sample accomplishment is merely to document for the committee that the work was formally recognized in the scientific literature. These accomplishments typically involved years and decades of work, and were based on the results of numerous projects led by various investigators building on each other’s work. Each example represents “putting in the last piece” of some portion of the puzzle, and was made

possible by the other pieces that were already in place, as evidenced by the lists of references cited in each of the supporting publications provided. There was no attempt made in Appendix 6 to provide anything remotely close to a comprehensive accounting of all contributing publications.

- Peer-reviewed articles published in the past 10 years based on VA research with dogs – these were assembled specifically in response to the request that we received after Meeting #2. Given the time required between completion of work with animals on an IACUC-approved protocol and publication of the results, as described above, these publications report on work with dogs that typically was “active” several years earlier than the dates of publication. We searched PubMed as well as checked through various lists that we have collected, of publications by VA investigators, so we believe that the publications that we provided to the committee include the most important ones.

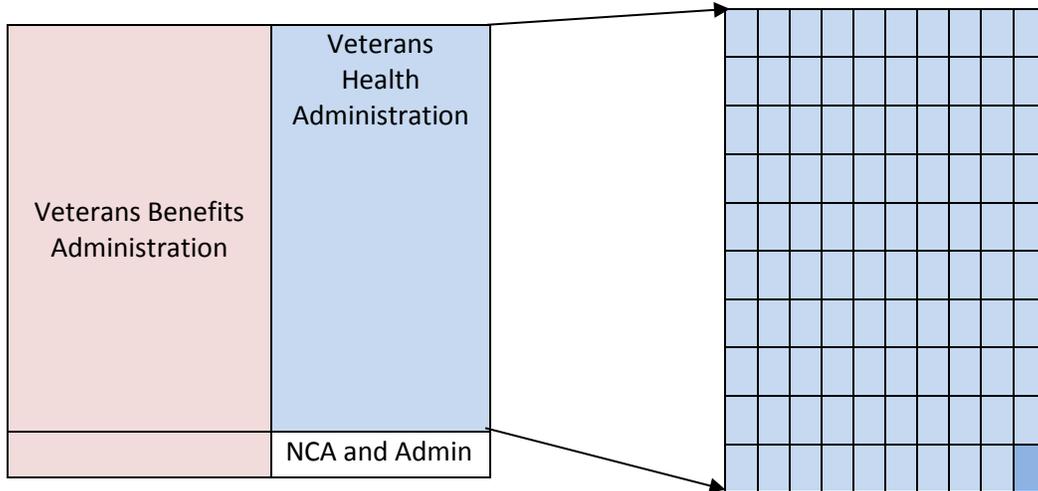
These publications were selected specifically to include only those that document some basis for considering the work to be “VA research” (affiliation of at least one of the authors with a VA station, acknowledged VA funding support, acknowledged use of other VA resources, etc.). This means that, for example, publications of related research conducted at other institutions, supported by NIH funding, and published by the same investigators at times when they did not hold VA appointments, were not included, even if they were obviously foundational to VA research that was published later or built on VA research that was published earlier.

Similarly, these publications were selected to include only those that reported research with dogs. Publications about VA research that did not involve dogs (new analyses of existing databases, work with human subjects, work with other species of animals) were excluded from this list, even though such work was certainly responsible for fitting in other pieces of the puzzle that the VA research with dogs also contributed to.

Effective modern biomedical research is at its core a combined effort of many investigators, each benefitting from and contributing to the efforts of the others. It is inconceivable that anyone today could identify a problem, develop and conduct the appropriate experiments to address it, and find the solution to the problem, all in isolation, without input from anyone else, and with the solution being so complete that no one else could possibly develop it further. Each result in biomedical research gives rise to the next questions to be addressed. Recognizing that VA research with dogs is part of such an ongoing, collaborative, and incremental process with a very long timeline will help in making sense of how various individual pieces of information about that research fit together.

It is entirely consistent with VA’s mission “To care for him who shall have borne the battle”, for VA to contribute to the effort to put together the jigsaw puzzle of how to provide better medical care for Veterans. Nevertheless, only a very small portion of the VA budget is dedicated to research. Over the past few years, roughly 60% of VA appropriations have been budgeted for the Veterans Benefits Administration. Of the other roughly 40% of VA appropriations, which were budgeted for the Veterans

Health Administration, only about 1% (0.4% of the total) has been budgeted for research. This is illustrated below:



How much money did VA have to work with altogether?

\$162,671,005,000 in FY2016 (9/1/15-8/31/16)

FY2016 Appropriations report

(<https://fas.org/sgp/crs/misc/R44625.pdf>)

\$ 91,422,152,000 for VBA

\$ 67,767,227,000 for VHA

\$ 271,220,000 for NCA

\$ 9,240,406,000 for VA admin

\$176,941,336,000 in FY2017 (9/1/16-8/31/17)

FY2017 Appropriations report

(<https://fas.org/sgp/crs/misc/R45047.pdf>)

\$105,589,085,000 for VBA

\$ 65,323,027,000 for VHA

\$ 286,193,000 for NCA

\$ 5,975,031,000 for VA admin

For FY2018 (9/1/17-8/31/18) Consolidated

Appropriations Act, 2018

(<https://www.congress.gov/bill/115th-congress/house-bill/1625/text>)

\$95,768,462,000 for VBA

\$ 1,962,984,000 for VHA, plus \$44,886,554,000 made available for VHA on 10/1/17

\$ 306,193,000 for NCA

About 1% of the VA budget for the Veterans Health Administration was appropriated for VA Medical and Prosthetics Research

\$630,735,000 in FY2016 (9/1/15-8/31/16)

FY2016 Appropriations report

(<https://fas.org/sgp/crs/misc/R44625.pdf>)

\$675,366,000 in FY2017 (9/1/16-8/31/17)

FY2017 Appropriations report

(<https://fas.org/sgp/crs/misc/R45047.pdf>)

\$722,262,000 in FY2018 (9/1/17-8/31/18)

(<https://www.congress.gov/bill/115th-congress/house-bill/1625/text>)

About 60% was for the Veterans Benefits Administration

Not quite 40% was for the Veterans Health Administration

A few % were for the National Cemetery Administration and administrative expenses

Roughly half of all research funded by VA (with the 0.4% of the total VA budget) is conducted with human subjects, and a few percent involve no living subjects at all (focused on new analyses of data in existing databases, research with tissues from tissue banks, computer modeling, engineering of new technologies, etc.).

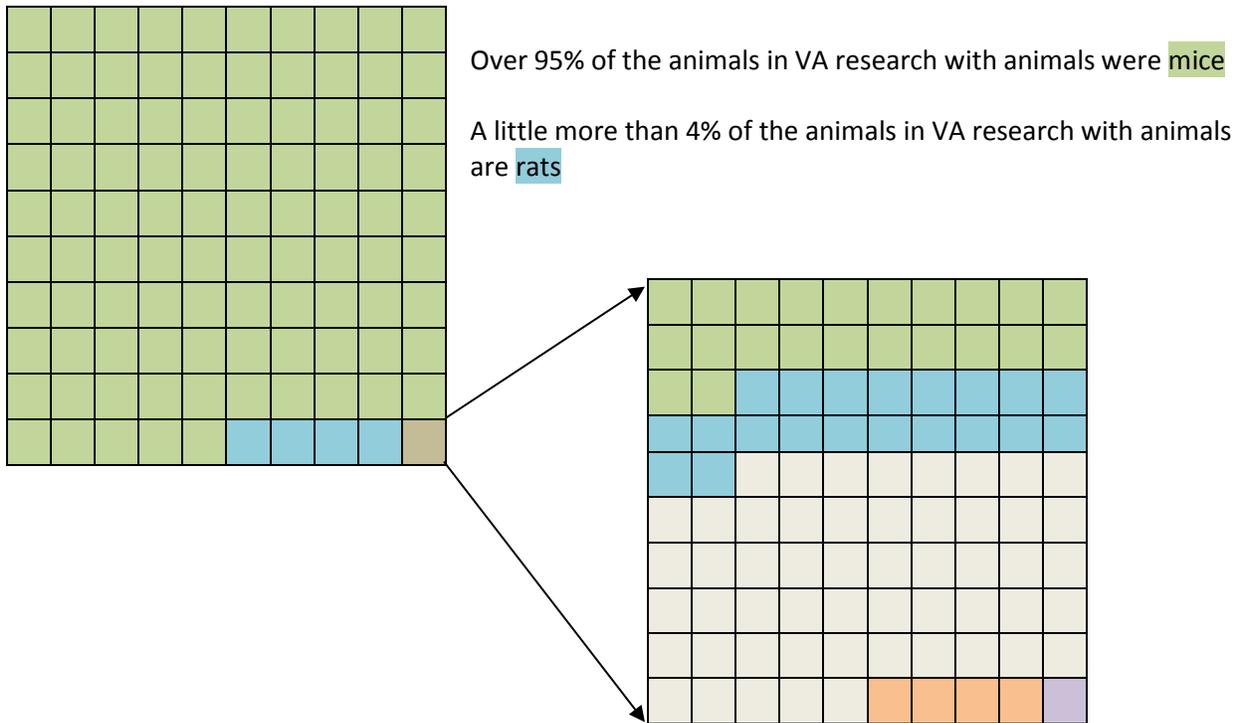
Specifically, among VA research projects newly selected for VA funding in FY2017 and FY2018 through 10/23/2018:

- 4.6% involved analysis of existing literature, tissue from tissue banks, or otherwise did not involve living subjects
- 55.9% involved human subjects
- 36.9% involved mice
- 9.9% involved rats
- Guinea pigs, hamsters, nonhuman primates, pigs, rabbits, and zebrafish were each involved in fewer than % of projects
- None involved dogs

The total is greater than 100%, because some projects involved more than one species of subjects. The exact proportions vary from year to year, depending on the specific research questions proposed for study. There are always far more questions that are important to address than there are resources available to address them at any given time, so selecting which of those important questions to study depends on (1) the findings of research done to date, (2) the development of new hypotheses and ideas for how to test those hypotheses, (3) the expertise of the investigators available to conduct the research, and (4) the availability of experimental methods that make it possible to make meaningful observations. Larger changes in the proportions of species involved can be seen over decades, but the general relationships shown here are representative of recent years, with some half of all VA research involving human subjects, most VA research with animals involving rats and mice, and very little VA research involving dogs.

VA research includes not only research funded by VA, but also research funded by other sponsors that is conducted on VA property, and research that may be funded by other sponsors and conducted off-site but is supported in some other way by VA resources. The proportions of animals by species in all of VA research are consistent with the proportions of research projects newly funded by VA recently. The exact numbers vary from year to year, according to the work being done, and the proportions may show larger changes over decades, but the general proportions are representative of recent years, with the vast majority of animals in VA research being rats and mice, and very few being dogs.

For example, the figure below shows the proportions of each species in VA research FY2017:



Within the last 1% of the animals in VA animal research, about 2/10 were more mice and about 2/10 were more rats, (this makes over 99% of all animals in VA animal research mice and rats) leaving 6/10 of that last 1% accounted for by all other species (frogs, rabbits, voles, swine, dogs, hamsters, gerbils, guinea pigs, cats, goats, nonhuman primates, and sheep). Dogs accounted for 4% of that last 1% (0.040% of all the animals), and cats (0.006% of the total) and nonhuman primates (0.004% of the total) together accounted for 1% of that last 1%.

Thus, VA research with dogs, which the committee has been asked to focus very narrowly on, is a very small portion of VA-funded research, which itself accounts for a very small portion of the whole of the VA budget. This specific focus is because the study that the committee is charged with conducting is necessitated by the focus of intense, emotion-driven public and media attention on this specific component of VA research. Nonetheless, it is critical for the committee to keep in mind that this specific component is only one element, albeit an important element, in the larger framework of VA research and VA's mission.

Following are our responses to the specific questions raised about the information that we have provided to the committee so far:

A. *In the attachment entitled "VA articles and appendix 6 table" we have provided specific comments for your consideration:*

- *Clarification of the connection of some of the papers to projects 27, 28 and 29*

Appendix 6 lists a sampling of specific “accomplishments” of VA research with dogs, not projects. These accomplishments were selected for inclusion because they represent easily recognizable medical advances. They generally reflect the synthesis of the findings of numerous projects, published in multiple reports covering different aspects of the findings. A publication may report on results from more than one protocol, and results from some protocols may be reported in more than one publication focused on different aspects of an overall project. The filenames of the publications provided with the accomplishments were designated as “Project XX” merely as shorthand to associate the publication with the accomplishment XX. As the accomplishments included in Appendix 6 are merely a sampling of the accomplishments of VA research, there is no reason to expect that every publication in the past 10 years about VA research with dogs must be linked to one of the examples included.

The full title of the Tan et al (2016) publication is “Impact of ventricular ectopic burden in a premature ventricular contraction-induced cardiomyopathy animal model”. The full title of the Jiang et al (2016) publication is “JPH-2 interacts with Ca_i -handling proteins and ion channels in dyads: Contribution to premature ventricular contraction-induced cardiomyopathy”. The full title of the Potfay et al (2015) publication is “Abnormal Left Ventricular Mechanics of Ventricular Ectopic Beats – Insights into Origin and Coupling Interval in Premature Ventricular Contraction-Induced Cardiomyopathy”. All three of these publications reference the supporting publication (Huizar, et al, 2011) that was provided with accomplishment 27 (“Showed that disturbances of heart rhythms can interfere with heart function, not just because of the rhythm but because of effects on how the heart muscle works”). This shows that these three publications build on research that contributed to accomplishment 27, which was the identification of a phenomenon. The titles of these three publications describe work to understand the mechanisms responsible for that phenomenon.

- *Connection of the 2 papers by Majerus et al to the appendix 6 list*

As the accomplishments listed in Appendix 6 are just a sampling of accomplishments of VA research with dogs, there is no reason that every publication of VA research with dogs in the last 10 years must be related to one of those examples. The two publications with Majerus as the first author address sensing and management of bladder pressure, which is an area for which no example happened to be included in Appendix 6.

- *Two unrelated papers on cardiac studies that we cannot connect to the appendix 6 list*

The full title of the Huang et al (2008) publication is “Proteasome inhibition 1 h following ischemia protects GRK2 and prevents malignant ventricular tachyarrhythmias and SCD in a model of myocardial infarction”. As the accomplishments listed in Appendix 6 are just a sampling of accomplishments of VA research with dogs, there is no reason that every publication of VA research with dogs in the last 10 years must be related to one of those examples. Although accomplishment 16 in Appendix 6 (“Developed some of the key instruments and techniques for ablation, a way to cure disturbances of heart rhythm that some 400,000 Veterans have, by selectively destroying abnormal heart tissue. This is now used routinely in the cardiac clinic.”) was the result of cardiac research conducted in Oklahoma City, there is no reason to expect that cardiac research conducted in Oklahoma City was limited to work related to that accomplishment. The research reported in the Huang 2008 publication describes mechanisms important to the management of consequences of myocardial infarction, which happens not to have been included in the list of sample accomplishments in Appendix 6.

The full title of the Singh et al (2013) publication is “Hypertrophy of Neurons Within Cardiac Ganglia in Human, Canine, and Rat Heart Failure: The Potential Role of Nerve Growth Factor”. As the accomplishments listed in Appendix 6 are just a sampling of accomplishments of VA research with dogs, there is no reason that every publication of VA research with dogs in the last 10 years must be related to one of those examples. The topic described by this title of this work associated with Hines, happens to be potentially related to accomplishment 29 in Appendix 6 (“Uncovered how Premature Ventricular Contractions disrupt the balance of the autonomic nervous system, which triggers more cardiac arrhythmias.”), from Richmond, in that the Singh et al publication reports on a mechanism that may contribute to autonomic imbalance. On the other hand, as the Singh et al publication considers autonomic imbalance in the context of heart failure, while accomplishment 29 addresses it in the context of cardiac arrhythmias, it must be recognized that the value Singh et al publication should not be limited to its relationship to accomplishment 29.

- *Three papers on ocular/corneal research from a group with active research on dogs that is not part of appendix 8*

The three Gronkiewicz publications are dated 2016 and 2017. This means that the active research with dogs reported in these publications was in all likelihood completed a few years before that. The publication of this work in 2016 and 2017 does not imply that there must be an IACUC-approved protocol currently in place and research with dogs currently being conducted. It is entirely plausible that Gronkiewicz et al are simply no longer involved in VA research with dogs, as indicated by the absence of such work from Appendix 8.

- *Three papers on oral/dental research from a group with active research on dogs that is not part of appendix 8*

The three publications on oral/dental research from Indianapolis are dated 2017, 2018, and (January) 2019. The senior author on all three publications is Barco. The research reported in these publications clearly required substantial work on the tissue samples collected. This means that the active research with dogs reported in these publications was in all likelihood completed a few years before the results were published. The publication of this work in 2017 - 2019 does not imply that there must be an IACUC-approved protocol currently in place for further research with dogs, and that there must currently be research being conducted with dogs. In fact, there has been no more research with dogs conducted by Indianapolis after 2014, and there is therefore no reason for any mention of such work in Appendix 8.

B. In the attachment entitled "relationship table" we ask you to clarify relations between projects in appendix 6 and 8

There is no reason to expect or require direct correspondence between each of the historical accomplishments listed in Appendix 6 and each of the currently active protocols included in Appendix 8, although it would be natural for the research on which the accomplishments in Appendix 6 were based to be further developed, potentially through currently active protocols in Appendix 8.

But Appendix 6 lists only a sampling of the historical accomplishments of VA research with dogs and is certainly not all-inclusive. In addition, the nature of biomedical research is such that new projects are always being developed, as new information, methods, technologies, and problems emerge. For both these reasons, it is completely reasonable that some current active protocols (Appendix 8) may not be directly related to any of the sample of historical accomplishments included in Appendix 6.

Likewise, there are any number of reasons that VA research with dogs that yielded important accomplishments in the past might not be the basis of currently active protocols for VA research with dogs – these could include simple logistics (e.g., retirement of the previous investigators, or continuation of the research by the same investigators at non-VA institutions, for example), changes in the best model to study as the research questions evolve (such as when previous findings justify proceeding to human clinical trials), changes in priorities (given that it is never possible for VA to fund all of the research that is worth doing at any given time), etc. Therefore, it is also completely reasonable that some of the historical accomplishments (Appendix 6) are not reflected in currently active protocols (Appendix 8).

C. Among the papers provided are a number from project 22, including one published in 2018 (Stimulation of abdominal and upper thoracic muscles). The primary author (and others) are in Edward Hines Hospital yet that facility is not listed among those with dogs. Could you clarify where that research is taking place?

For a publication to be dated 2018, the research with dogs would in all likelihood have to have been completed a few years earlier. The authors of those publications were affiliated with Hines and acknowledged that affiliation in their publications, but research with dogs at Hines ended in 2016. Between 2016 and 2018, it is quite reasonable to assume that the authors were working with the data gathered earlier, when the IACUC-approved procedures were carried out with dogs. There is no reason that research with dogs must be currently ongoing for a report about research with dogs to have been published in 2018. Hines does not have any currently active VA research with dogs, and so is not included in Appendix 8.

D. *In two instances approvals of protocols are not given by the VA IACUC but by other IACUCs:*

d-1: in the 2018 paper by Ruaengsri et al (in Appendix 6, project 25) it is stated that approval was given by the Washington U IACUC (under Surgical technique, pg 1873)

d-2: in the 2014 paper by Zheng et al (provided today) it is stated that approval was given by the UAB IACUC (ethics statement in methods).

Could you explain to us the reason these studies that were funded by the VA were not approved by a VA IACUC?

The failure to mention in publications that the protocols were approved by the VA IACUC does not document that the VA IACUC failed to approve the protocols. These may have reflected journal policies (limiting mention to only one institutional approval), or simple omissions. As described in the introduction to the packet of VA Canine Documents that we provided to the committee for Meeting #1, VA policy requires that work funded by VA may only proceed with approval by the VA IACUC, and this is documented in the Just-In-Time database, which ensures that VA funding is not released for research with animals until after the VA IACUC approval has been granted, and the protocol has cleared all required secondary review and approval procedures.

In the case of the Ruaengsri et al (2018) publication, it appears that the work was done with NIH support at Washington University. The publication was provided as a supporting document for accomplishment 25 because it acknowledges VA funding support of Dr. Melby, one of the co-authors. This acknowledgement recognizes Dr. Melby's having been awarded VA funding, with a funding start date of 1/1/17. Dr. Melby indicates an institutional affiliation with Washington University on this publication. The Ruaengsri et al publication was received by the journal on 1/10/18. This all suggests that the procedures with dogs reported in this publication were all complete before Dr. Melby was awarded VA funding, which makes it entirely appropriate that the VA IACUC would not have been involved in overseeing the protocol for the procedures with dogs. Dr. Melby most likely contributed to the work with dogs before he was awarded VA funding, and his involvement after being awarded VA funding was as a scientific collaborator in the analysis, interpretation, and reporting of the results. The VA funding that was awarded to Dr. Melby starting in 2017 is for a project that includes research with dogs, which has been approved by the VA IACUC, but has not yet begun, and is not part of the work reported in the Ruaengsri et al publication.

The Zheng et al (2014) publication was included in the list of VA research with dogs published in the last 10 years because several of the authors indicate affiliation with the Birmingham VA, and Dell'Italia acknowledges support by a VA award. The award number given in the publication refers to an award for which funding began on 1/1/14, so this was the support that was in place at the time of publication. Dell'Italia was also awarded VA funding earlier (funding start date 10/1/09), which supported the project that was reported in this publication about VA research with dogs. The VA IACUC approval of that work was granted in August 2009.

Do you have a road map that connects the 42 papers you sent us to the projects in Appendix 6? Could you share it with us please? It would be immensely helpful for us.

There is no reason to assume that each of the 42 publications reporting VA research with dogs in the past 10 years must be related to at least one of the sample of historical accomplishments included in Appendix 6, or that each of those sample accomplishments must each be related to at least one of the 42 reports of VA research with dogs published in the last 10 years. This is particularly true because we specifically tried to avoid repeating in the list of 42 any of the publications that we had already provided in support of the accomplishments in Appendix 6 (there is one duplication). Of course, some of the 42 are related to some of the accomplishments included in Appendix 6, but some report work that happened not to be included in Appendix 6, and some of the accomplishments in Appendix 6 were reported more than 10 years ago.

