University of California, Los Angeles
Chancellor's Animal Research Committee (ARC)

Continuation Application

General Information

Title:	[redacted]
Protocol #:	[redacted]
PI:	[redacted]
Status:	APPROVED_WITH_CODICIL
Approval Period:	3/12/2019-3/11/2020
Received Date:	3/4/2019
Type:	Continuation
Species:	20 Dog (Pain Category D)
Create Date:	2/28/2019 9:20:18 AM
Created By:	[redacted]
Owner:	[redacted]

Updated Sections

- Continuation Summary
- Number of Animals Used
- Pain Literature Search
- PI Assurance
- Pre-Review

Personnel Certifications Due:

[redacted]
- MHQ (val d until 1/23/2020)
- Species Specific Training for Dog

[redacted]
- MHQ (val d until 1/17/2020)

Notes:

- General Certif cation Test: Offered through CITI program (**http://www.citiprogram.org**). Please ensure your affiliat on is listed as UCLA and complete the Animal Research Basic Course.
- Medical History Questionnaire (MHQ): Offered by the Occupat onal Health Facil ty (**http://mhq.healthsciences.ucla.edu/**).
- Species Specific Training: Please visit the DLAM webs te: **https://portal.dlam2.ucla.edu/EducationTraining/Pages/default.aspx**.

For more questions regarding certifications/training, please visit:
http://ora.research.ucla.edu/rsawa/arc/pages/certification_info.aspx.

Codicil(s):

- The Committee understands that [redacted] will not handle or perform procedures with Dogs until Species Specific Training for Dogs has been completed. Please contact DLAM Clin cal veterinarian Dr. [redacted] ([redacted]) or DLAM Training (dlamtraining@research.ucla.edu) when this species is available so that you can receive this training. -

Continuation Summary

Please provide the appropriate information regarding changes to this protocol. Then update the respective sections.

1. Will you be planning on making changes to this protocol? If you answer "yes" to this question, please address Questions 2 and 3 and update the appropriate sections that are affected by these changes. Please note that you are not required to update every section of your protocol.

○ Yes ◉ No

2. Check the following if you will be making any of the following changes:

In addition to checking these boxes, you must update the respective sections of this protocol.

- ☐ Protocol title
- ☐ Funding or funding agency
- ☐ Principal investigator
- ☐ Co-investigator
- ☐ Personnel
- ☐ Location

3. Indicate if you will be making any Significant changes to the following:

In addition to checking these boxes, you must update the respective sections of this protocol.

- ☐ Animal species and/or strain
- ☐ Number of animals
- ☐ Pain category
- ☐ Method of euthanasia
- ☐ Experimental procedures

A. If you indicated that you will be changing the number of animals above, please provide a detailed explanation of your rationale for the number of additional animals requested. Please note that if this request for additional animals also entails a change in experimental procedures and/or pain category, please update these application sections and indicate these changes on this page.

n/a

B. If you indicated that you will be changing the experimental procedures above, please provide a detailed explanation of

how this change in experimental procedures relates to the experiments in your currently approved protocol. In addition, please clarify what results you hope to yield from this change in experimental procedures.

n/a

4. **In order to assist reviewers, briefly describe in lay terms the changes you are making and complete the appropriate sections.**

n/a

5. **To assist the ARC in documenting scientific progress arising from use of animals under this protocol, please provide ONE of the following:**

- ○ Citation(s) of presentations or articles resulting from this protocol (either accepted or submitted). Please include an abstract.
- ◉ A brief (1-2 sentence) update regarding progress made toward achieving the scientific objective(s) of this protocol.
- ○ A copy of the most recent annual progress report submitted to the funding agency.

If the scientific progress documentation is in a text format, please paste (or type) it here. Otherwise, you will need to submit it to the ARC as a hard copy.

We would like to keep this protocol open, as we are currently discussing potential projects for this protocol.

6. **Please indicate whether any adverse effects or unanticipated problems have been experienced, including higher than anticipated mortality/morbidity regardless of the cause. If so, please provide an explanation of how these events/problems were resolved.**

No

7. **Please respond to the following questions regarding alternatives to the use of animals. If you answer YES to any of these items, please explain.**

A. Have any alternatives become available since the previous ARC approval that could replace the use of animals to achieve your research and/or teaching goals?

No

B. In order to reduce potential pain/distress, have any procedural refinements been made since the previous ARC approval?

No

C. Has the number of animals required for the study been reduced since the previous ARC approval?

No

Number of Animals Used

List the species and the total number of animals used in the previous year.

Species	Total Number Used
Dog	0

Research Summary

Your answers to the questions on this page determine the other sections needed to be filled out.

1. **What is the Title of the Project?**

Teaching, training and evaluation of stents, coils, catheterizations and embolization techniques for the treatment of aneurysms & vascular malformations.

2. **Check all that apply:**

- ☐ Tumor Formation (spontaneous or implanted)
- ☑ Chronic Disease (diabetes, EAE, status epilepticus, etc.)
- ☑ Tissue Collection (blood and all other tissues, including those collected after euthanasia)
- ☐ Antibody/Ascites Production
- ☑ Surgical Procedures (survival, non-survival)
- ☑ Non Surgical Procedures (injection of experimental drugs, behavioral studies)
- ☑ Gas Anesthetic Agent(s) (use of isoflurane, halothane, etc)
- ☑ Hazardous Agents (carcinogens, paraformaldehyde, rDNA, vectors, etc.)
- ☐ Radioisotopes or radioactive implants
- ☐ Prolonged Physical Restraint (physical restraint of unanesthetized animals for periods longer than 15 minutes)
- ☐ Genetically Modified Animals
- ☐ Tissue Sharing (use of tissues only)

3. Will the research be conducted exclusively on tissue received from another investigator?

No

If yes, do your funding sources require an ARC approved protocol?

No

4. Check all that apply:

☐ Experiments done entirely at another institution

NOTE: For experiments conducted entirely at another institut on please subm t the most recent approval not ce and a copy of the most recently approved protocol from the other institution with your submission. Please also indicate the PHS Assurance number and AAALAC accreditation status.

☐ Experiments done entirely at VAGLAHS

☐ Program Project/Training Grant

Administrative approval only – no animals associated with this protocol.

☐ Breeding Colony: #

NOTE: If you will be breeding animals for this protocol and do not already have an approved breeding protocol on file w th the ARC, you must submit an Appl cat on to Establish and/or Maintain a Breeding Colony at this time. Check the box above but leave the "Breeding Colony Number" field above empty. The ARC Staff will update the Breeding Colony Number following the submission of a breeding colony application.

5. If you are seeking approval for a training grant, list all individual projects supported by the program project or training grant, including the principal investigators' names and their current ARC approval numbers. If no animal research is currently being supported by the overall grant, please assure the Committee that, should an investigator of a project covered by the overall grant initiate research involving animals, ARC approval will be obtained prior to the distribution of funds.

Personnel

There can be only one Principal Investigator per protocol. To edit a person's contact information or add a new person to our system, click on the People tab above.

Prior to the submission of an amendment to add personnel, please ensure that these individuals have completed all applicable animal use certification requirements and have a Medical History Questionnaire (MHQ) on file with the Occupation Health Facility (OHF). If you are only requesting the removal of personnel, please email the ARC administrative office (arc@research.ucla.edu). An amendment application is NOT required if you are only removing personnel.

Principal Investigator

[redacted] View Person Detail

Email:	[redacted]	UID:	[redacted]
Phone:	[redacted]	Degree:	[redacted]
Fax:	[redacted]	Dept:	[redacted]
Status:	Faculty		

What role will this person be performing in this protocol?

Principal Investigator

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

Yes

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

Dr. [redacted] is an Associate Professor of [redacted] who has extensive experience with interventional catheterization procedures in the canine model since [redacted]

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

Dr [redacted] is a specialist in the field of [redacted] will conduct the teaching and/or testing sessions and teach various endovascular techniques to internal and extramural physicians and investigators. [redacted] will be involved in diagnostic interventional procedures that use angiography, CT or MRI.

Will this person handle radioactive materials or radioactive animals?

No

Co-Investigator

[redacted] View Person Detail

Email:	[redacted]	UID:	[redacted]
Phone:	[redacted]	Degree:	[redacted]
Fax:		Dept:	[redacted]
Status:	[redacted]		

What role will this person be performing in this protocol?

Co-Investigator

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

Yes

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

[redacted] has experience in a laboratory animal setting. [redacted] has experience in swine handling and anesthesia in the [redacted] Labs since [redacted] will be responsible for animal care, anesthesia, monitoring and euthanasia.

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

[redacted] will be coordinating the laboratory scheduling and will assist with laboratory procedures as necessary. [redacted] will be responsible for animal care, anesthesia monitoring, handling, transfer, and euthanasia.

Will this person handle radioactive materials or radioactive animals?

No

Personnel

[redacted] View Person Detail

Email:	[redacted]	UID:	
Phone:	[redacted]	Degree:	
Fax:		Dept:	[redacted]
Status:			

What role will this person be performing in this protocol?

Personnel

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

Yes

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

[redacted] was trained to preform the surgical creation of aneurysms at the [redacted] been involved with this research model since [redacted]

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

[redacted] will perform the aneurysm creation in this protocol.

Will this person handle radioactive materials or radioactive animals?

No

Personnel

[redacted] View Person Detail

Email:	[redacted]	UID:	[redacted]
Phone:	[redacted]	Degree:	[redacted]
Fax:	[redacted]	Dept:	[redacted]
Status:	Faculty		

What role will this person be performing in this protocol?

Personnel

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

Yes

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

Dr. [redacted] is a Professor of [redacted]
who has extensive experience with interventional catheterization procedures in the canine model since [redacted]

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

Dr. [redacted] is a specialist in the field of [redacted] [redacted] will conduct the teaching and/or testing sessions and teach various endovascular techniques to internal and extramural physicians and investigators. [redacted] will be involved in diagnostic interventional procedures that use angiography, CT or MRI.

Will this person handle radioactive materials or radioactive animals?

No

Personnel

[redacted] View Person Detail

Email:	[redacted]	UID:	[redacted]
Phone:	[redacted]	Degree:	
Fax:		Dept:	[redacted]
Status:	[redacted]		

What role will this person be performing in this protocol?

Personnel

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

No

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

[redacted] has experience in swine handling and anesthesia in the [redacted] Labs since [redacted] [redacted] will be responsible for animal care, anesthesia, monitoring and euthanasia. [redacted] has been trained in angiography and endovascular procedures by physicians in the department of [redacted]

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

[redacted] will be responsible for animal care, anesthesia, monitoring, handling, transfer and euthanasia.

Will this person handle radioactive materials or radioactive animals?

No

Personnel

[redacted] View Person Detail

Email:	[redacted]	UID:	[redacted]
Phone:	[redacted]	Degree:	[redacted]
Fax:		Dept:	[redacted]
Status:	[redacted]		

What role will this person be performing in this protocol?

Personnel

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

Yes

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

[redacted] completed a B.S degree in [redacted] from [redacted] [redacted] is licensed in [redacted] by the [redacted] as well as the [redacted] as well as holding a [redacted] license from [redacted] [redacted] is trained on the [redacted] angiography system, both in general operations as well as 3D post-processing. [redacted] clinical experience has been at [redacted] in angiographic and cardiology procedures. [redacted] has been trained to support angiography and endovascular procedures performed by physicians in the Department of [redacted]

[redacted] has completed the species specific training with Dr [redacted] [redacted] will review [redacted] Lab procedure and equipment SOP's. Following review of SOP's [redacted] will complete proficiency training with Dr [redacted] [redacted] will also receive hands on training from experienced [redacted] staff on a variety of procedures that are required to support our research needs.

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

[redacted] will be assisting physicians with radiographic equipment operations, tableside assistance, animal preparation, handling and monitoring, as well as archival of radiographic images, scheduling and documentation of procedures. [redacted] will be operating the angiography, CT, US or MRI imaging systems.

Will this person handle radioactive materials or radioactive animals?

No

Personnel

DLAM Staff View Person Detail

Email:		UID:	[redacted]
Phone:	[redacted]	Degree:	
Fax:		Dept:	DIV LAB ANIMAL MEDICINE
Status:	Staff		

What role will this person be performing in this protocol?

Personnel

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

Yes

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

N/A

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this

protocol.

DLAM personnel may assist with canine handling, anesthesia and heath monitoring in the [redacted] Labs.

Will this person handle radioactive materials or radioactive animals?

No

Personnel

[redacted] View Person Detail

Email:	[redacted]	**UID:**	[redacted]
Phone:	[redacted]	**Degree:**	[redacted]
Fax:	[redacted]	**Dept:**	[redacted]
Status:	Faculty		

What role will this person be performing in this protocol?

Personnel

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

Yes

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

Dr. [redacted] is a physician trained in [redacted] and has been working with the animal aneurysmal with swine models for several years. Dr [redacted] has been working with canine models for several years in [redacted] and [redacted] has been working with canine at [redacted] since [redacted]

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

Dr. [redacted] is a specialist in the field of [redacted] will conduct the teaching and/or testing sessions and teach various endovascular techniques to internal and extramural physicians and investigators. [redacted] will be involved in diagnostic interventional procedures that use angiography, CT or MRI.

Will this person handle radioactive materials or radioactive animals?

No

Personnel

[redacted] View Person Detail

Email:	[redacted]	**UID:**	[redacted]
Phone:	[redacted]	**Degree:**	
Fax:		**Dept:**	[redacted]
Status:	[redacted]		

What role will this person be performing in this protocol?

Personnel

Which species will this person handle in this protocol?

Dog

Will this person handle animal tissue in this protocol?

No

Will this person be involved with Survival Surgery Procedures?

Yes

Will this person handle rDNA and/or infectious materials?

No

Will this person handle highly toxic chemicals and/or carcinogens?

Yes

Please provide a brief account of the person's qualifications and experience with the animal model(s) and procedures in this protocol. Please include a description of any experience obtained beyond the required ARC/DLAM training courses. If this individual does not have any relevant previous experience, please briefly describe how he or she will be trained in the specific research techniques.

[redacted] has experience in animal handling and anesthesia in the Department of [redacted] and [redacted] Labs since [redacted] will be responsible for animal care, anesthesia, monitoring and euthanasia. [redacted] has been trained in angiography and

endovascular procedures by physicians in the department of [redacted]

Please list the duties (including specific procedures to be performed, as appropriate) that this person will perform involving live animals under this protocol.

[redacted] will be responsible for animal care, anesthesia, monitoring, handling, transfer and euthanasia.

Will this person handle radioactive materials or radioactive animals?

No

Contacts

Name:	[redacted]
Contact Type:	Emergency, Administrative
Home Phone:	
Mobile Phone:	[redacted]
Email:	[redacted]

Name:	[redacted]
Contact Type:	Emergency, Administrative
Home Phone:	
Mobile Phone:	[redacted]
Email:	[redacted]

Funding

1. Funding Types (Check All That Apply):

- [x] Department
- [ ] Extramural
- [ ] UCLA Academic Senate
- [ ] Gift
- [ ] No funding at this time
- [x] Other: External collaborators

Rationale

1. Provide a non-technical summary of the overall objectives of the study.

The overall objective of this protocol will be the training, teaching and evaluation of multiple endovascular devices and techniques.

To treat intracranial aneurysms in human is a delicate procedural techniques. They include passing microcatheters through tiny/ fragile vessels at which point coils and/or stents are deployed through these catheters. To train the interventional neuroradiologists who just started learning how to use these devices or other interventionalists who will start using new devices on the patients, special training will be provided by the experts in this field.

Since in vitro experiments have various limitation to simulate the clinical settings, large animal is required for trainees to experience the treatment methods before they performed on human patients.

Visiting faculty, [redacted] residents and fellows are trained in the techniques of cerebral microcatheterization, coil, embolization (GDC etc.), stents and glue/particle embolization.

2. Indicate the possible benefits to mankind and/or animals or the advancement of knowledge that may be derived from this study.

By teaching more physicians the techniques of [redacted] more patients worldwide can benefit from these procedures, which provide less invasive methods for treating neurovascular diseases. Because many of these techniques and devices are pioneered and tested at [redacted] the [redacted] department is highly qualified to train other physicians.

3. Explain the rationale for the use of animals, including (a) why the chosen species is the most appropriate for the study and (b) why the chosen species cannot be replaced with a phylogenetically lower species. Note that cost cannot be accepted as a justification.

Dogs are necessary because in vitro models cannot simulate the nature of the arterial wall defects (elasticity, ease of perforation, vasospasm), coagulation system and flow dynamics ocurring inside the aneurysms. Moreover, dogs have very similar coagulation system and the vascular anatomy and size can simulate the anatomy of the human vasculature, which make them a good model to simulate real aneurysms.

Especially because these physicians are being trained to perform these techniques in human cerebral circulation, it

is crucial that the training session simulate the clinical situation as closely as possible.

The canine aneurysm model, especially bifurcation type, has been thought to be most appropriate for preclinical evaluation of aneurysm. [redacted] The bifurcation aneurysm procedure is achievable in swine, but the size/length of the carotid limits the reproducibility of the model. Therefore the canine bifurcation model is the only aneurysm model that can be reliably used for chronic aneurysm treatment and evaluation.

Side wall type aneurysm, especially swine model, has a tendency to occlude and heal quickly with or without embolization. In general human cerebral aneurysm arises at the bifurcated portion, and the hemodynamical difference from experimental side wall aneurysm is often viewed with suspicion. Since many factors are involved to evaluate the feasibility, such as flow dynamics, thrombogenetic or thrombolytic system, and immune system, it is necessary to use dog models.

Moreover, phylogenetically lower species cannot replace the use of canine. This is because considering the hemodymanic effect, thrombogenicity, and anatomical similarity required in the endovascular procedure, it is impossible to substitute this role with phylogenetically lower experiments.

Experimental Design & Justification for Requested Number of Animals

1. Provide a two- to four-sentence lay description of the experimental procedures written in language easily understandable to a seventh grade student.

This protocol will be used for the teaching and training of interventional techniques and to evaluate existing, new, or improved medical devices. Teaching and training will be done with [redacted] who are just starting to learn how to use these devices and/or experienced interventionalists who will begin using new devices in clinical patients. Teaching and training will be provided by experienced faculty and/or industry experts in this field.

2. Provide a complete description of: (a) all activities involving the use of research animals; (b) a scientific justification for the total number of animals required to conduct this study. The number of animals justified in this section must match the totals in the Pain Category Assignments. To the extent possible, assign all animals to experimental groups, which can be easily distinguished by the independent variables defining each group (e.g.,drug dosages, time points, controls, etc.). Clearly indicate the number of animals needed per group and explain how group sizes were determined, either(i) by statistical analysis, or (ii) where statistics are not applicable (e.g., teaching labs, feasibility studies, antibody production, etc.), on the basis of other considerations (e.g., student/animal ratio, tissue yield per animal, antigen/animal ratio, prior experience, etc.). If statistical analysis is employed to determine the number of animals required, please specify the statistical method used.

In this protocol, conditions will be created in the dog to simulate vascular malformations and occlusions that will be treated with devices commonly use in human medicine (i.e. coils, stents, catheters, clot retrieval devices and liquid embolic agents).

The devices for evaluation may be second generation devices that have had design improvements and/or a supplemental device that works in conjunction with a commercially approved device already in the clinical environment. Other aspects of a device evaluation will be to gain further understanding of the ease of deployment in the target organ, structural integrity of the device once deployed, or to evaluate the characterizes of the device once it has been deployed in a live system; does it migrate, do vascular changes occur, etc.

The measurable outcomes of each evaluation will depend on the device, location of deployment, and the interventional procedure. Examples of possible outcomes could be: does the device perform in tortuous vessels in the brain, are there measurable histological changes in the vessel at the site of deployment in an aneurysm, does a new device deploy as easily as a device already in clinical use, and/or does a new device cause hemodynamic changes that need to be evaluated in line with a potential outcome of an interventional procedure looking at clot formation or clot retrieval.

Device and/or procedure evaluations, or teaching & training events will occur under the guidance of a practicing physician and a junior faculty member and/or client. The procedure evaluation will be conducted by a practicing physician to, or with, internal or extramural practicing physicians and/or clients.

There are no animal groups. The animals may not all undergo the exact same procedure, depending on what the physician and/or trainees need to learn, etc.

Typically statistics are not used for the assessment of devices, it is a qualitative assessment of device performance compared to a device already approved by the FDA. In our experience 1-3 animals are used in these studies.

In our experience 20 animals may be used over 3 years. We have allocated 4 animals for acute procedures and 16 animals for chronic procedures.

We expect to perform 2 sessions/year, with 1-4 animals/session. If the training session is teaching a catheterization procedure, device deployment and/or retrieval, there are numerous arteries which can be used which allows for more than one person to be taught/session. This approach will reduce the number of total number of animals required for this protocol.

Chronic animals may be maintained from 3 to 180 days post procedure (standard recovery periods: 7, 14, 28, 60, 90, 180 days).

Acute: One angiography day (teaching, training, device evaluation), with euthanasia occurring the same day.

Chronic: Initial angiography day (teaching, training, device evaluation) or aneurysm surgery, followed by recovery of the animal at the end of the procedure. Device implant or follow-up angiography would then occur between 3-180 days, with euthanasia occurring after the final angiography session.

Typical procedures will use one device and/or a combination of devices. Examples: 1) a stent will be deployed in the vessel over a surgically created aneurysm to evaluate natural occurring thrombosis inside the aneurysms pocket, or 2) a stent will be deployed in the vessel over a surgically created aneurysm followed by the deployment of a coil or liquid embolic agent into the aneurysm pocket to speed up action of thrombosis.

We estimate the "use" numbers base on our core users previous study requests. Each device, teaching event, training procedure and/or target organ dictate how the device training and/or evaluation is assessed.

1-4 dogs/lab

1-3 trainees/lab: we may use as few as 1 animal for up to 3 trainees.

1-8 devices/lab: this will depend on the number of animals, number of target organs, number of aneurysms, or the procedures trained or evaluated.

1-3 procedures/device: this will depend on the number of "passes" that are available for a specific target organ. Example: a new interventional catheter or guide wire can be re-positioned in multiple vessel site throughout the body, were as, a new coil or stent can only be deployed once in an aneurysm or in the rete.

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Procedures that result in either acute or chronic events.

1) Microcatheterization:
Microcatheters are small catheter used to deliver either coil shaped or liquid materials into a target vessel(s) or organ(s).

2) Detachable Coil:
A coil shaped materials made of pure platinum. They are deployed into the aneurysm cavity to occlude and treat them.

3) Glue/Particle/Liquid embolic agent:
Embolic materials used in the treatment of vascular malformations.

4) Embolization:
Insertion of various substances into the circulatory system to obstruct specific blood vessels

5) Clot Retrieval:
Devices designed to remove and/or aid in the removal of blood clots.

6) Aneurysm Creation & Embolization:
Experimental side-wall or bifurcation aneurysms will be created on the bilateral common carotid arteries. A variety of embolization techniques (coils, stents, embolic agents, or glue/particles) may be implemented to obtain the required result. Chronic aneurysms will be created 10-14 days prior to embolization. The bifurcation aneurysm in the dog is the preferred model. The bifurcation aneurysm in the swine model is not reliable due to anatomical restrictions.

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All animals with aneurysms (acute or chronic) will receive daily anti-platelet therapy of Aspirin 81mg, and Plavix 0.5-1mg/kg to prevent antithromboembolic complication due to the deployed interventional devices [redacted] Anti-platelet therapy will be started at least 3 days before the aneurysm creation and continue until the terminal procedure.

Depending on the histologic findings obtained from the earlier time points, minor changes regarding evaluating the later time point might be required based on the earlier results. However; total number will not be changed. The number of animal is decided based on our previous procedural performance and/or histological findings. Individual tissue sample will be histologically analyzed. Multiple stains may be performed on each specimen based on our previous experimental data.

All animals will be obtained from USDA approved commercial vendors.

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All chronic procedures will be scheduled following veterinary consultation, that this consultation will include a clear plan of action that will ensure procedures are discussed, the time-line is clear, and the amount of times procedures are conducted is finalized.

Visiting faculty, [redacted] residents and fellows will learn how to use the endovascular devices under the supervision of trained experts in the field. Specifically we will teach the basic procedure with several tips, associated with glue/particle embolization for arteriovenous malformation model, and coil embolization for the aneurysm model.

All visiting physicians not listed in the Personnel section will complete a MHQ prior to working with animals and will be escorted by approved personnel when conducting activities described on this protocol.

In addition, vendor demonstrations will also be performed under this protocol. The vendor will send a list of vendor personnel to [redacted] Management as well as brief description of what they will do with the animals and how they are qualified/experienced with the techniques. A Senior Veterinarian in DLAM, will be made fully aware of these situation and will make sure that this protocol is thoroughly followed by vendor and its personnel.
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Pain Category Assignments

NOTE: A painful procedure is defined as any procedure that would reasonably be expected to cause more than slight or momentary pain and/or distress in a human being to wh ch that procedure is applied. Examples of potentially painful/distressful procedures include, but are not lim ted to the following: terminal surgery; exuberant inflammation from adjuvants; ocular and skin irritancy testing; food or water deprivation beyond that necessary for normal presurgical preparation; noxious electrical shock that is not immediately escapable; paralysis or immobility in a consc ous animal; extensive irradiation.

Category	Description
C	Momentary or no pain/distress (Examples: injections of non-toxic substances; peripheral blood collections not requiring anesthesia; euthanasia and harvesting of tissue only; observing natural behavior; behavioral testing without signif cant restraint or noxious stimuli.)
D	Pain/distress relieved by use of appropriate anesthetics, analgesics, tranquilizers or by euthanasia (Examples: terminal surgery; survival surgery; retro-orbital blood collection; euthanasia of animals showing signs of more than slight or momentary pain and/or distress.)
E	Pain/distress can not be relieved by use of anesthetics, analgesics, or tranquilizers, as the use of these agents would interfere w th the experimental design (Examples: pain research; toxic ty testing.)

Species:	Dog
Strain or Breed (if applicable):	Mongrel or Beagle
Average Weight:	20-30 kg
Sex:	Mixed
Pain Category:	D
Previous Number of Animals Approved:	20
Change in Number of Animals Needed (+/-):	0
Number of Animals Needed for the 3 Year Period:	20

Pain Category

1. If the animals are listed under Pain Category D and/or E, check below all criteria that will be used to assess any potential pain/distress/discomfort in the animals. If applicable, include criteria used to evaluate post-operative pain/discomfort.

- [x] Restlessness
- [x] Vocalizing
- [x] Decreased or impaired mobility
- [ ] Conjunctivitis, corneal edema, photophobia
- [x] Licking, biting, or guarding a painful area
- [ ] Failure to groom, unkempt appearance
- [ ] Open sores/necrotic skin lesions
- [x] Loss of appetite
- [x] Weight loss.
  Percentage weight loss (max allowable 20%): 10%
- [x] Other: Signs of pain during the procedure: increased heart rate and respiration

2. If the animals are listed under Pain Category E, please specify the pain/distress/discomfort experienced by animals as a result of the experimental manipulations and provide scientific justification indicating why pain/distress/discomfort-relieving methods will not be employed in this protocol.

NOTE: Procedures that may cause more than momentary or slight pain or distress to the animals must be performed with appropriate sedatives, analgesics or anesthet cs, unless withholding such agents is justified for scientific reasons and will continue for only the necessary per od of time.

The following questions must be answered for animals listed under Pain Category D and/or Pain Category E. Federal Regulations require that investigators consider alternatives (the 3 Rs - replacement, refinement and reduction) to procedures that may cause more than momentary or slight pain or distress to animals.

3. Consider all the alternatives listed below and explain why each of the following is not an available alternative for the proposed potentially painful/distressful procedure.

A. Replacement of animals with non-animal models (e.g., in vitro procedures, computer model) or a phylogenetically lower species:

Extensive testings have already been performed using in-vitro aneurysm models, but in-vitro models cannot simulate the coagulation system, and flow dynamics of the aneurysms. Dogs tend to be thrombolytic, and can provide a good approach for mechanical evaluation and recanalization of this device.

Glass and rubber models of blood vessels do not simulate closely enough the human arterial system. It is crucial for trainees to get a realistic feel of pushing catheters through living arteries with blood flow. Trainees should be comfortable pushing catheters and deploying devices while knowing the limitations of the arteries.

In vivo models are essential to the evaluation the mechanical property of material for training, physical response and histological findings. The complexities of the host response to the materials cannot be mimicked in phylogenetically lower animals because their physiology is so different from humans.

B. Please discuss why the procedures cannot be further refined in order to minimize potential pain and/or distress to animals:

Unnecessary surgical dissection will be avoided, and appropriate anesthesia and analgesia will be given to minimize animal pain or distress. Our procedure will employ the surgically created aneurysm. The skin incision and muscle dissection will be minimized so that we can minimize the surgical invasion and shorten the operation time. Since this is a surgically created model, we can't avoid surgery in this protocol. Assessment in the ch[illegible]

necessary and survival surgery can't be avoided.

If arterial cut-down is performed, the vessel will be surgically repaired or ligated as necessary.

A total of 3 aneurysms (two on common carotid artery and one at the junction of connected artery) may be created to maximize data collection from each animal and reduce animal usage.

C. Reduction in the number of animals proposed in this application (e.g., fewer animals involved in potentially painful procedures):

There are no animal groups. We will perform teaching and training of interventional procedures or evaluation of new devices. Not all of our procedures will be exactly the same.

The animals may not all undergo the exact same procedure, depending on what the physician and/or trainees need to learn. We expect that 24 animals be used over 3 years. We expect to do 2 sessions/year, with 1-4 animals/session. If the training session is teaching a catheterization procedure, device deployment and/or retrieval, there are numerous arteries which can be used which allows for more than one person to be taught/session. This approach will reduce the number of total number of animals required for this protocol.

Pain Literature Search

The following questions must be answered for animals listed under Pain Category D and/or Pain Category E.

Please note that according to PHS Policy IV.C.1.a, the Guide for the Care and Use of Laboratory Animals (the Guide p. 10) and USDA Animal Welfare Act Regulat ons §2.31(d)(1)(i) "procedures involving animals will avoid or minimize discomfort, distress, and pain to the animals." Further, in order to meet the above-ment oned regulatory requirement and in accordance with UCLA's Animal Welfare Assurance on file w th the National Institutes of Health Off ce of Laboratory Animal Welfare (OLAW), the Committee must ensure that the "principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has prov ded a wr tten narrative descript on of the methods and sources used to determine alternatives were not available." Please also note that the Comm ttee recommends the use of keywords that are specif c to the painful/distressful procedures you will be conducting and the animal model that will be used.

1. Indicate at least two databases or other sources consulted to support the conclusion that appropriate alternatives are not available.

- [x] Pubmed (Medline)
- [ ] PsychINFO
- [ ] Altweb
- [ ] UC Center for Alternatives
- [ ] Animal Welfare Information Center
- [x] BIOSIS
- [ ] Current Contents
- [ ] Other:

2. Combination of keywords used during the search:

Please specify the keywords used in the box below, including 1) the specific painful procedures that you are conducting, 2) the animal model being used and 3) alternative terms (e.g., animal model, welfare, pain, stress, distress, methods, *in vitro*).

Please see the following examples, noting that the keywords listed only apply to a protocol involving these experimental variables:

Mouse and chronic implant and in vitro model
Mouse and artery ligation and pain
Mouse and sleep deprivation and welfare

Keywords used:

Dog AND aneurysm AND alternative (21 hits)
Dog AND pain AND angiography AND aneurysm (2 hits)
Dog AND embolization AND pain (8 hits)
Dog AND aneurysm AND pain (7 hits)
Dog AND aneurysm AND pain AND distress (0 Hits)
Dog AND aneurysm AND embolization (125 hits)
Dog AND aneurysm AND embolization AND stent(29 hits)
Dog AND embolization AND alternative animal model (8 Hits)

3. Date of most recent search (MM/DD/YYYY):

NOTE: The l terature search must be updated whenever experiments that may cause potential pain or distress are proposed/modified. The literature search must also be updated at the time of each three-year renewal, and should be conducted within 2 months of submission.

2/28/2019

4. Years Covered (e.g., 1980-2019):

1975-2019

Animal Care

1. Will the experiments involve tumor formation?

The ARC requires daily monitoring of tumor growth.

No

2. Will the experiments involve chronic disease (e.g., diabetes, chronic seizures, infections with disease agents) or a chronic condition (e.g. headcaps, implants)?

Yes

3. Will the experiments involve other procedures that may lead to potential complications (e.g., surgical procedures, administration of compounds with potential toxic effects)?

Yes

4. For all types of experiments, if animals may experience complications, please describe the criteria for premature euthanasia below.

Criteria for premature termination of animals: Dog will be euthanized if the aneurysm ruptures and causes respiratory distress, significant hemorrhage or any sign considered to be associated with post surgical complication. Post-operative hemorrhagic complication will be evaluated with clinical signs of dyspnea and swelling in the area surrounding the surgical incision. Any complications will be reported to the veterinary staff immediately, and termination will be based on their recommendation. In addition to these criteria, premature euthanasia will be assessed with response to loss of appetite, weight loss greater than 10%, infection at the surgical site that does not respond to antibiotic treatment, or evidence of pain that does not respond to analgesic therapy.

Given the situation of thrombus complications after the surgical procedure, we may use a Merci clot retrieval system to try to eliminate the thrombus causing the adverse clinical signs. If clot retrieval is unsuccessful and premature euthanasia is required, we will administer vet grade euthanasia solution (pentobarbital) via intravenous injection.

For initial medication calculations will will require current body weight measurements. For chronic animals, we will require monthly body weight measurements for accurate medication calculations.

If more frequent imaging is required or the animals show a decrease in body weight associated with clinical observations or decrease in body weight, we will request additional body weight measurements.

5. Check below all that apply to convey special animal care requirements to the responsible veterinary staff.

- ☐ Temperature Range(s)
- ☐ Humidity
- ☐ Light Cycles
- ☐ Bedding/Litter changing schedules
- ☐ Water (e.g., sterile or deionized)
- ☐ Special diet/Feeding schedule
- ☐ Deprivation of food and/or water for reasons other than surgical preparation

6. If you checked any of the boxes above, explain special care requirements in detail.

7. Environmental Enrichment: UCLA vivarium staff provide environmental enrichment to all species (please refer to the **ARC Policy on Environmental Enrichment**).

a. If you request to provide additional or alternative environmental enrichment, please describe the environmental enrichment below.

b. Please provide scientific justification if your research precludes the use of environmental enrichment.

Chronic animals must be singly housed for 10-14 days post-surgery, so that they don't accidentally traumatize each others surgical sites. Following the 10-14 day recover period from a procedure, the animals can be co-housed until the terminal procedure date. In the event we have a single animal housed in [redacted] we will stimulate the animal with increased human interaction by either [redacted] staff and/or DLAM staff.

8. If you will be using transgenic animals in this research, please clarify whether there are any anticipated or suspected phenotypes of the transgenic mice that might cause pain or discomfort to the animals. If any pain, distress, or morbidity is associated with the phenotypes of this line, please indicate the criteria for premature termination of these mice.

9. PLEASE COMPLETE IF YOU HAVE MICE AND/OR RATS IN DLAM-MANAGED FACILITIES. Please check one response to the following:

I request that the veterinarian (or his/her designee) euthanize animals found to be sick or injured for me:

◉ I request that the DLAM veterinarian (or his/her designee) euthanize my animals for me in accordance with his/her veterinary discretion at the time that they are found sick or injured. This decision will only apply to animals in cages that I've marked with a green euthanasia sticker on the cage card. DLAM will notify me of the euthanasia by email after the fact.

I understand that I remain responsible for monitoring of my animals, in accordance with my approved protocol and with the ARC Policy on ***Responsibility for Monitoring Laboratory Animals***.

I will treat or euthanize animals:

○ I assure the ARC that I will promptly respond to Veterinary Health Case notifications regarding my animals, as required by the ARC Policy on ***Notification of Investigators with Sick or Injured Animals***.

Locations

Please indicate ALL locations where animals will be housed and/or used, including:

1. **Vivarium Housing** (where animals will be housed). Please note that if vivarium housing has not been assigned, select "VIVARIUM" as the building name and "Unassigned" as the room number.
2. **Study Area** (any investigator-maintained facility outside the vivarium where USDA-covered species will be housed for per ods longer than 12 hours, or where non-USDA-covered species will be housed for per ods longer than 24 hours).
3. **Research Area** (where non-surg cal activities, including euthanasia, will be performed).
4. **Surgery Area - Survival** (where recovery surgery will be performed).
5. **Surgery Area - Non-Survival** (where terminal surgery will be performed).

Building	Room	Species	Location Type
[redacted]	[redacted]	Dog	Surgery Area - Survival **Reason:** Survival surg cal procedures
[redacted]	[redacted]	Dog	Research Area **Reason:** MRI imaging will be done here
[redacted]	[redacted]	Dog	Surgery Area - Non-Survival **Reason:** Ang o room
[redacted]	[redacted]	Dog	Surgery Area - Survival **Reason:** Ang o room
[redacted]	[redacted]	Dog	Surgery Area - Non-Survival **Reason:** Ang o room
[redacted]	[redacted]	Dog	Surgery Area - Survival **Reason:** Ang o room
[redacted]	[redacted]	Dog	Surgery Area - Non-Survival **Reason:** CT room
[redacted]	[redacted]	Dog	Surgery Area - Survival **Reason:** CT Room
[redacted]	Unassigned	Dog	[redacted] **Reason:** Housing rooms were classified as "unassigned" because animals on chronic studies may be moved from room to room in [redacted] based on the census and availabil ty of space.

Medications and Experimental Drugs

List below all medications/drugs/compounds/agents/etc. that will be given to the animals. Please be sure to include analgesics, anesthetics, antibiotics and all experimental drugs or treatments. Cell lines injected in suspension should be listed here.

The select on of the most appropriate med cation/agent should reflect that which best meets clin cal and humane requirements w thout compromising the scientific aspects of the research protocol. In accordance w th federal regulat ons, consultat on with an attending veterinarian is required in the planning of a research protocol involving procedures that may cause more than momentary or slight pain or distress to the animals. The **ARC Policy on Use of Pharmaceutical-Grade Compounds** requires that investigators use pharmaceut cal-grade compounds whenever they are available, even in acute procedures.

If pharmaceut cal-grade preparations are not available, please dentify wh ch compounds are affected and provide supporting justification in your Experimental Design. All non-pharmaceutical-grade drugs must be filter-sterilized pr or to use.

Please do not list euthanasia drugs in this section.

Drug/Compound Name:	Buprenorphine
Species:	Dog
Medication Type:	Analges c
Dose or Concentration:	0.01-0.03 mg/kg
Volume:	Baased on body weight
Frequency:	every 8-12 hours for 48 hours
Route:	sc
Length of treatment/administration:	every 8-12 hours for 48 hours post surgery then as need
Purpose:	Pre-Operative/Intra-Operative Post-Operative

Drug/Compound Name:	Buprenorphine-SR
Species:	Dog
Medication Type:	Analges c
Dose or Concentration:	0.06-0.2 mg/kg
Volume:	Based on body weight
Frequency:	every 48-72 hours
Route:	sc
Length of treatment/administration:	every 48-72 hours
Purpose:	Pre-Operative/Intra-Operative Post-Operative

Drug/Compound Name:	Carprofen
Species:	Dog

Medication Type:	Analges c
Dose or Concentration:	4mg/kg
Volume:	based on body weight
Frequency:	once a day
Route:	other: SC or oral
Length of treatment/administration:	48 hours post surgery
Purpose:	Pre-Operative/Intra-Operative Post-Operative

Drug/Compound Name:	Meloxicam
Species:	Dog
Medication Type:	Analges c
Dose or Concentration:	0.1-0.2 mg/kg
Volume:	based on body weight
Frequency:	once a day
Route:	other: IM, SC or PO
Length of treatment/administration:	48 hrs post surgery
Purpose:	Pre-Operative/Intra-Operative Post-Operative

Drug/Compound Name:	Isoflurane
Species:	Dog
Medication Type:	Anesthet c
Dose or Concentration:	1-3%
Volume:	N/A
Frequency:	continuous
Route:	inh
Length of treatment/administration:	duration of procedure
Purpose:	Pre-Operative/Intra-Operative

Drug/Compound Name:	Lidocaine
Species:	Dog
Medication Type:	Anesthet c
Dose or Concentration:	1 mg/kg
Volume:	based on body weight
Frequency:	once per surgery
Route:	sc
Length of treatment/administration:	once per surgery
Purpose:	Pre-Operative/Intra-Operative

Drug/Compound Name:	Midozolam
Species:	Dog
Medication Type:	Anesthet c
Dose or Concentration:	0.1-0.5 mg/kg
Volume:	based on body weight
Frequency:	Once
Route:	im
Length of treatment/administration:	Once during induction
Purpose:	Pre-Operative/Intra-Operative

Drug/Compound Name:	Propofol
Species:	Dog
Medication Type:	Anesthet c
Dose or Concentration:	2-10 mg/kg
Volume:	based on body weight
Frequency:	once
Route:	iv
Length of treatment/administration:	slow IV inject on
Purpose:	Pre-Operative/Intra-Operative

Drug/Compound Name:	Cefazolin
Species:	Dog
Medication Type:	Antib otic
Dose or Concentration:	20mg/kg
Volume:	based on body weight
Frequency:	every 2-3 hours during surgery
Route:	iv
Length of treatment/administration:	30 minutes before surgery
Purpose:	Pre-Operative/Intra-Operative

Drug/Compound Name:	Aspirin
Species:	Dog
Medication Type:	Other
Dose or Concentration:	81mg
Volume:	One tablet
Frequency:	once a day
Route:	oral
Length of treatment/administration:	beginning three days before endovascular procedure and continuing for the duration of survival
Purpose:	Pre-Operative/Intra-Operative Post-Operative Other: Thromboprophylaxis

Drug/Compound Name:	Heparin
Species:	Dog
Medication Type:	Other
Dose or Concentration:	1000-3000 IU
Volume:	1-2 ml
Frequency:	as needed to maintain ACT around twice baseline
Route:	iv
Length of treatment/administration:	duration of procedure
Purpose:	Pre-Operative/Intra-Operative

Drug/Compound Name:	N troglycerin
Species:	Dog
Medication Type:	Other
Dose or Concentration:	200 mcg diluted into 2 mL of saline
Volume:	1-5 mL
Frequency:	once or twice
Route:	other: IA
Length of treatment/administration:	During procedures
Purpose:	Pre-Operative/Intra-Operative Other: vasodilat on

Drug/Compound Name:	Omnipaque
Species:	Dog
Medication Type:	Other
Dose or Concentration:	300mg/ml
Volume:	20-40ml
Frequency:	During imaging
Route:	other: IA and/or IV
Length of treatment/administration:	during the operat on only
Purpose:	Pre-Operative/Intra-Operative

Drug/Compound Name:	Onyx and Precipitating Hydrophobic Injectable L quid (PHIL)
Species:	Dog
Medication Type:	Other
Dose or Concentration:	N/A
Volume:	determined by aneurysm size (0.5-3 mL/ aneurysm)
Frequency:	once
Route:	iv
Length of treatment/administration:	N/A
Purpose:	Other: embolic agent

Drug/Compound Name:	Papaverine
Species:	Dog
Medication Type:	Other
Dose or Concentration:	3mg/ml
Volume:	1ml
Frequency:	as needed
Route:	other: intra-arterial
Length of treatment/administration:	as needed
Purpose:	Other: for vasospasm

Drug/Compound Name:	Plavix
Species:	Dog
Medication Type:	Other

Dose or Concentration:	0.5-1mg/kg
Volume:	based on body weight
Frequency:	once a day
Route:	oral
Length of treatment/administration:	beginning three days before endovascular procedure and continuing for the duration of survival
Purpose:	Pre-Operative/Intra-Operative Post-Operative Other: Thromboprophylaxis

Euthanasia

For each species used, please provide the euthanasia information. Techniques for euthanasia must follow guidelines established in the AVMA Guidelines for the Euthanasia of Animals: 2013 Edition.

1.Species:

Dog

2.How will animals be euthanized?

Non-Physical Method

3.For animals that will be euthanized by a physical method, please indicate that method (decapitation or cervical dislocation).

a. Please indicate the appropriate physical method.

Other:See #4 below

b. Will anesthesia be used prior to use of the physical method of euthanasia?

No

c. If anesthesia cannot be administered, please provide scientific justification.

4.For animals that will not be euthanized at the end of the study, please indicate the final disposition.

Critical organs are harvested immediately after euthanasia. The animals will be observed for lack of a heartbeat and respiration and for graying of mucous membranes for at least 10 minutes to confirm death to comply with the AVMA Guidelines for the Euthanasia of Animals: 2013 Edition.

Euthanasia Medications

List the drug(s) used for euthanasia on an animal by physical or non-physical methods.

Please note that according to the AVMA Guidelines for the Euthanasia of Animals: 2013 Edition, "compressed CO2 in cylinders is the only recommended source of carbon dioxide because the inflow to the chamber can be regulated precisely. Carbon dioxide generated by other methods such as from dry ice, fire extinguishers, or chemical means (e.g., antacids) is unacceptable."

Drug Name:	Vet grade 390 mg/mL pentobarb tal sodium plus 50 mg/mL of phenytoin sodium
Species:	Dog
Dose or Concentration:	1-2 mL/10 pounds of body weight
Route:	iv
Purpose of Drug:	Euthanasia

Tissue Collection

Please enter the following information regarding tissue collection for the protocol. See ARC Policy on Blood Collection from Laboratory Animals.

1. Tissue To Be Collected:

☑ Blood

☑ Other Collected: artificial aneurysm or other surgically created structures or target organs/vessel(s) & devices.

2. Frequency of blood and/or other tissue collections:

Treated aneurysm will be harvested after euthanasia.

Blood - We may collect blood during the angiography procedure to measure ACT levels and/or other hematological parameters (glucose, hematocrit, organ enzymes, CBC, etc.)

Tissue - If required, following euthanasia and confirmation of death.

Tissues for possible collection: surgically created aneurysms and/or malformations, vessels, rete, brain, lungs, liver, kidney (x2), spleen, sex organs, thymus and adrenal glands.

3. Volume of blood and/or other tissue collected per time point:

Aneurysm on the parent artery. 0.5-5ml of blood is collected not to exceed a maximum of 1% of the animal's body weight per week.

Blood - We may collect small amounts of blood (0.5-2ml) necessary to test Activated Clotting Time (ACT) or other hematological parameters.

4. Describe techniques that will be used to collect blood and/or other tissue.

Standard methods of the surgical removal of the aneurysm on its parent artery will be utilized.

If blood is needed, we will draw it from either the cephalic, saphenous, femoral vessels, or the anterior vena cava. 0.5-2 ml of blood is collected not to exceed a maximum of 1% of the animal's body weight per week.

Vascular endothelial cells may be collected for histological analysis to evaluate for any changes in the vessels associated with device deployment and/or retrieval. The device, which includes the endothelial cells, will be removed through the femoral sheath and placed in a appropriately sized conical tube. The tubes will be transferred to the research lab for evaluation.

5. Describe how anemia and infection will be prevented.

Anemia and/or infection are not expected. However, in the case an animal develops symptoms that suggest otherwise, a veterinarian will be consulted and recommended treatment will be followed.

Surgical Procedures and Post-Operative Care

Please complete the following questions, noting that any requested exception to ARC Policy must be justified in the space provided.

Note: ARC pol cy requires investigators to employ the following measures to ensure asepsis while conducting survival surgery: asept c surg cal techniques; asept c surg cal field; sterile instruments; clean lab coat/surg cal gown; and sterile surg cal gloves. *For information on surgeries on rodents and birds, please see the* ***ARC Policy on Survival Surgery in Mice, Rats and Birds***.

Non-survival surgeries of extended durat on or procedures otherwise likely to increase the risk of Intraoperative infection and/or sepsis (e.g. gastrointestinal surgery) will be evaluated on a case-by-case basis to determine whether aseptic techn ques must be used. Refer to the **ARC Policy on Non-survival Surgical Procedures** for further informat on.

Please note that surgical records are required for all animals. These records must include anesthetic administration and intra-operative mon toring, as well as post-operative recovery observations, including administration of analgesics and antib otics and suture/staple removal if appl cable. Additionally, any adverse outcomes must also be recorded.

1. Pre-Operative care will include (check all that apply):

- ☐ Lab tests
- ☐ Conditioning
- ☑ Fasting: 12-16 hrs
- ☐ Other:

Please note that a phys cal examinat on is required.

2. Will neuromuscular blocking agents be used (e.g., Pancuronium, Succinylcholine)? Refer to the ARC Policy on Neuromuscular Blocking Agents.

No

3. Select all criteria that will be used to assess the proper level of anesthesia.

The level of anesthesia should be assessed on a continuous basis.

- ☑ Respiration rate
- ☑ Heart rate
- ☐ EEG
- ☐ EKG
- ☑ Muscular relaxation
- ☑ Positive toe pinch
- ☐ Corneal reflex
- ☑ Color of mucous membranes
- ☑ Other:

Temperature & signs of pain. Pain signs will be monitored as movement in response to toe pinch or increasing heart rate.

4. Surgical preparation of all mammalian species must include:

1) Removal of hair w th #40 clipper blade in a wide margin around the incis on site.
2) Three alternating scrubs using a germ cidal scrub and 70% alcohol.
3) Placement of lubricating ointment into the eyes.
4) Covering the animal except the surgery site w th a sterile drape.
5) Placing the animal on an external heat source (water circulating heat pad or heating pad set on "low" with a barrier placed between the animal and the heating pad).

◉ I assure the ARC that surgical preparation will be performed as outlined above.

○ *Not applicable, as this protocol includes only non-survival surgeries for which aseptic technique is not required.*

PLEASE NOTE: Any deviation from the policies above must be detailed and scientifically justified in the space below.

5. Indicate the methods to be employed to prevent (a) hypothermia and (b) dehydration (including volume of fluids and route). If this question is not applicable to the proposed surgical procedures, provide a brief explanation.

To prevent hypothermia, the veterinarian recommends the use of water-circulating heading pads over heating lamps and/or electr cal heating pads. The use of heating lamps is strongly discouraged. If not used properly, heating lamps and electrical heating pads may cause thermal injury to the animal. Therefore, describe precaut ons taken to prevent hyperthermia.

Baseline of 5-10 ml/kg/hr of saline or Lactated Ringers Solution (LRS) infusion will be used, and rate will be adjusted as needed based on blood pressure and blood loss.
Circulating warm water and/or warmed air system will be utilized during surgery so that thermoregulation is readily maintained at appropriate levels.

6. Surgical preparation of the surgeon must include:

1) Wash hands w th germicidal soap.
2) Sterile gloves.
3) Surgical Mask.
4) Cap and booties (not required for mice and rats)
5) Sterile gown (clean lab coat or gown acceptable for m ce and rats)

◉ I assure the ARC that surgical preparation will be performed as outlined above.

○ *Not applicable, as this protocol includes only non-survival surgeries for which aseptic technique is not required.*

7. Instrument preparation must be performed by:

1) Autoclave sterilization or ethylene oxide (gas) sterilizat on.
2) Either chemical disinfect on (acceptable between multiple surgeries in mice, rats, and non-mammalian species) or
3) Hot bead sterilizer.

◉ I assure the ARC that instrument preparation will be performed using one of the methods outlined above.

○ *Not applicable, as this protocol includes only non-survival surgeries for which aseptic technique is not required.*

8. Duration of Surgical Procedures (Must be completed as applicable):

For non-survival surgery, ind cate the duration from anesthesia induction to euthanasia. For survival surgery, ind cate the durat on from anesthesia induction to recovery from anesthesia.

Survival: 5-7 hours
Non-Survival: 1-5 hours

9. Provide scientific justification for performing multiple survival surgeries on a single animal.

Multiple survival surgeries will be approved only when they are related components of the experimental design.

Survival Surgery 1: aneurysm creation.
Survival Surgery 2: device deployment.
Survival Surgery 3 or 4: femoral cut-down procedure, if percutaneous puncture is not possible, for follow-up angio.

The chronic aneurysm creation will be performed approximately 2-4 weeks prior to the interventional procedure to enable healing to occur. When possible, animals will undergo no more than 3 survival procedures.

The justification for multiple surgeries is, 1) to establish the surgically created aneurysm and allow sufficient time for the surgical area to heal, 2) to deploy an interventional device using fluoroscopy in the aneurysm and/or target organ that will mimic a clinical condition our physicians/trainees would encounter in the human patient, 3 or 4) to perform follow-up angiography to ensure the device remains in the treatment area.

10. Please describe all surgical procedures, including non-survival procedures.

Survival surgery (chronic) procedures will be performed aseptically.

Non-survival surgery (acute) procedures will be performed in a clean environment.

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Canine will be transported through DLAM managed corridors to the [redacted]Lab awake. An IV catheter will be placed into the cephalic or saphenous vein for delivery of medications, fluids, and/or contrast agents. Once the IV catheter is in place, they will sedated using Propofol or a combination of Ketamine & Midazolam to achieve the appropriate level of anesthesia for intubation and arterial catheter placement. Following sedation the canine will receive the appropriate dose of Carprofen and Buprenorphine for the prevention of pain and inflammation. Isoflurane is used as a gas anesthetic agent to maintain the appropriate level of anesthesia throughout the procedure. Both acute and chronic events will follow this anesthesia protocol. Post-operative care will include Buprenorphine every 8-12 hours for 48 hours and Carprofen or Meloxicam once daily for 48 hours.

Under general anesthesia, an appropriately sized femoral sheath will be inserted into the target femoral artery. From here the teaching/training/evaluation will be conducted depending on the purpose.
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IV catheter is placed in either the cephalic or saphenous veins for delivery of medications, fluids, and/or contrast agents.

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Surgical Aneurysm Creation:
Chronic surgery procedures will be performed aseptically. We will proceed with the betadine swabs first, followed by alcohol wipes, for 3 times prior to the surgery. Bilateral 8cm incisions will be made lateral to the sternohyoid muscle in the neck. Through one of these incisions, the external jugular vein will be isolated, ligated, and removed for construction of the vein pouch. This pouch will constitute the aneurysm(s). The common carotid arteries will then exposed by opening the carotid sheaths. They will be clamped both proximally and distally. A bifurcation or sidewall anastomosis will be made utilizing the exposed carotid arteries and the vein pouch. Left CCA is ligated and clamped and tunneled under trachea. Once this is done an arteriotomy is created in Right CCA. Using a series or running sutures the arteries will be anstomsed along with the ligated external jugular vein to create the vein pouch. The vascular clamps will be removed and hemostasis will be assured. The skin incisions will be closed using a multi-layer subcutaneous technique with absorbable suture. The animal will be allowed to recover for at least 10-14 days post aneurysm surgery prior to using the aneurysm for testing of endovascular devices, materials or imaging. A total of 1-4 aneurysms is possible in this model: 1-4 sidewall aneurysm on the common carotid (2/carotid), or 1 sidewall aneurysm on common right carotid artery only and 1 aneurysm at the junction of connected artery will be created. The aneurysms will be created during a single anesthesia event.

Implant procedure (2-4 weeks later)
Once the surgical creation of the 1 to 3 aneurysm is completed, procedure will be shifted to the endovascular treatment of the aneurysms. Heparin will be given intravenously. An appropriate size vascular access sheath will be inserted in the femoral artery and a catheter will be advanced through the sheath, and positioned near the aneurysm. Angiography using Omnipaque is performed to confirm the aneurysm shape, and any potential vasospasm. In the event of a vasospasm, Papaverine or Nitroglycerin can be delivered intra-arterially to the site of the aneurysm to reduce or eliminate the vasospasm. Through the catheter, a stent device will be deployed in the parent artery across the neck of the aneurysm. Next, through the stent mesh, a small catheter will be advanced into the aneurysm, and multiple platinum coils or a liquid embolic agent will be deployed into the aneurysm. The same procedure will be repeated for the other aneurysms.

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For the training/testing of materials, which were developed for the treatment of brain arteriovenous malformation, surgical creation of experimental arteriovenous malformation (AVM) model will be used.

Surgical creation of experimental arteriovenous malformation (AVM) model:
Using one of the neck incisions the carotid and ipislateral jugular vein are isolated and the side to side anastomosis will be created between these vessels under the microscope. This procedure produces the artery-venous shunt and modifies the hemodynamic environment. Since this vessel structure presents anatomical similarity to the human arteriovenous malformation, it is used as a simulated vessel malformation.

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Stents:
A catheter will be directed to the experimental aneurysms where stents will be placed in the each common carotid artery across the neck of the created aneurysm, and one stent will be placed across the neck of the aneurysm located at the junction of bilateral common carotid artery. Then, under fluoroscopy, a small catheter will be advanced into each created aneurysm through the mesh of each stent, and platinum coils will be deployed into the aneurysm. The each aneurysm will be completely packed with deployed coils, and the coils will stay inside of the aneurysm as the stent prevent the herniation of the deployed coils.

Coil Embolization:
A catheter will be directed to the experimental aneurysms and coil(s) will be deployed via the catheter until occlusion can be confirmed.

Glue/Particle/Liquid Embolic Embolization:
A catheter will be directed to the experimental aneurysms or a target organ/vessel and liquid embolic/glue/particle will be injected via the catheter until occlusion can be confirmed.

Clot Retrieval Devices:
The catheter will be advanced through the aorta and positioned in the target vessel (e.g common carotid, ascending pharyngeal, lingual, facial, internal maxillary arteries). An artificially created thrombus will be deployed into the target vessel. After confirming complete occlusion of the vessel, a clot retrieval device (metal basket like device) will be developed to capture the thrombus occluding the vessel. It will be advanced over the thrombus to retrieve it. Same procedure will be performed on the contralateral side. Devices will be advanced and assessed by themselves if a thrombus is not deployed. The clot is left in place for roughly 5 min-1 hr before it is retrieved . One vessel will be occluded at a time. After the clot is retrieved, we shall proceed to another vessel. Both sides of a paired vessel will not be occluded at same time.

Solitaire (fully retrievable, self-expanding stent-like design) or Merci (helical shape) clot retrieval procedure:
A angiogram will be obtained via the microcatheter to confirm the position of the thrombus at the occlusion site. Next, a Solitaire or Merci clot retriever will be deployed distal to the clot. The balloon catheter tip will be inflated with 0.8 mL of 50% contrast solution. If the tip of the catheter is nearly-occlusive/occlusive at the origin of the vessel, the balloon will not be inflated. Then, an attempt will be made to pull the thrombus into the guiding catheter while gently aspirating. When the retriever system is immediately outside the guiding catheter, ~30 mL of blood will be vigorously aspirated while removing the clot retrieval device. As in the clinical environment, no more than 6 attempts will be made to retrieve the thrombus.

Endothelial Cell Collection:
In some procedures, devices will be deployed and retrieved without a thrombus present. Devices deployed will be evaluated for their impact on the vessels into which they are deployed. The device will be positioned against the target vessel wall. Once deployed, the device will stay in the vessel for 5-10 minutes before retrieving the device. The device, which includes the endothelial cells, will be removed through the femoral sheath and placed in
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a appropriately sized conical tube. The tubes will be transferred to a research lab for evaluation.

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Cut-down Procedure:
Cut-down procedure will be utilized at initial embolization and possible for follow-up angiography. Under aseptic conditions, we will make a 1-3 cm incision in the groin. The femoral artery is identified and isolated. The vessel is ligated distally and a arteriotomy is performed to introduce the vascular sheath. After the interventional procedure is completed, the sheath is removed and the vessel ligated. The femoral artery will be repaired with 7-0 Prolene or ligated with 2-0 silk. Femoral artery repair or ligation procedure will be performed on every dog.

Next, the surgical incisions will be closed using absorbable sutures layer by layer. The skin will be closed using absorbable suture in a subcuticular pattern. (intradarmic suture fashion).

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Following the initial procedure, we may evaluate the anesthetized dog with diagnostic modalities such as US, CT or MRI.

All medications/drugs used on this protocol will be pharmaceutical grade.

We will use multi modal analgesia: Buprenorphine, Carprofen and lidocaine pre & post operatively.

Buprenorphine (sustained released or regular formulation) will be used pre and post operatively (for at least 24 hours) for all survival surgical procedures.

Carprofen or Meloxicam will be administered pre-operatively.

Cefazolin will be administered as an antibiotics agent.

Lidocaine (local anesthetics) will be injected subcutaneously in the groin before the incision is made over the femoral artery.

Heparin is administered throughout the procedure to avoid clotting due to vessel catheterization and device deployment.

Nitroglycerine or Papaverine may be use as vasodilators in the event a vessel spasm is encountered while manipulating the target vessels. They will be delivered intra-arterially to the site of the spasm.

Baseline Activated Clotting Time (ACT) is measured at the beginning of the study and after each dose of heparin to maintain coagulation levels not higher than three times the base line.

Terminal procedure will be performed under general anesthesia. After all procedures are complete, animals will be sacrificed with an intravenous injection of veterinary grade euthanasia solution.

11. Please indicate the suture materials to be used:

- [x] Internal: absorbable sutures (e.g., Dexon, Vicryl)
- [ ] External: non-absorbable skin sutures (e.g., Nylon, wound clips). *Please note that external skin sutures or wound clips must be removed 7-14 days following surgery.*
- [ ] Other/not applicable (describe below):

12. During recovery from anesthesia, what indications will be monitored to assure the animals are stable?

In accordance with the Guide for the Care and Use of Laboratory Animals, particular attent on should be given to thermo-regulation, card ovascular and respiratory function, and post-operative pain or discomfort during recovery from anesthesia.

Heart rate and respiration, tempreture will be monitored during recovery from the surgery. Animals will be observed continuously until ambulatory.

Temperature support will be provided using blankets and/or electronic temperature support system (Baer Hugger). Temperature will be monitor using an electronic/digital temperature probe.

13. How often will animals be monitored after anesthetic recovery?

The ARC requires that animals be observed continuously by trained personnel during the immediate anesthet c-recovery period (i.e., until the animal is ambulatory) and at least daily after anesthetic recovery. However, post-operative mon toring frequency may be greater depending on the complex ty of procedures involved, administration of post-operative analgesia, and the species of animal used.

Post-operative animals will be observed for clinical signs twice daily for 2 days. Animals will be observed daily for morbidity and/or mortality, until the terminal sacrifice.

Species Surgery

Species:	Dog
Number of Animals:	4
Surgery Type:	Nonsurvival Surgery
Surgeries per Animal:	

Time Between Surgeries:	

Species:	Dog
Number of Animals:	16
Surgery Type:	Multiple Survival Surgery
Surgeries per Animal:	3
Time Between Surgeries:	2-4 weeks

Non-Surgical Procedures

1. Describe the basic methods used for all non-surgical manipulations (e.g., imaging, behavioral studies, Parkinson's and diabetes induction, chronic implant maintenance, cannulation).

Percutaneous femoral artery access:
With the animal anesthetized in dorsal recumbency, the region of the femoral artery will be palpated and the skin overlying the artery will be clipped as needed and prepared with alternating betadine and alcohol scrubs. A puncture needle will be used to access the femoral artery percutaneously and an appropriately sized sheath will be placed into the femoral artery using Seldinger technique. The sheath will be used to place a catheter into the artery. Once the catheter is removed, the sheath will be removed from the artery and the site will be held off for a minimum of 5-10 minutes to ensure adequate hemostasis.

If percutaneous approach to the femoral vessel is technically not feasible for any of the procedures outlined above, we will perform a surgical cut down procedure as outlined in the Surgical Section.

Angiography:
A catheter and guidewire will be introduced through the femoral artery and navigated to the common carotid artery. Contrast will be injected (i.e. Omnipaque) to visualize the anatomy of the blood vessels and patency of the constructed aneurysm and/or the target vessel/organ.

CT Angiography:
Under general anesthesia, we will transfer a canine to the CT room. A contrast agent (omnipaque) will be injected into the vein and CT will be performed to visualize the flow of contrast material through the vessels, focusing on the site of the aneurysms and/or target vessel/organ.

MRI Scanning:
Under general anesthesia, we will transfer a canine to the MRI room. A contrast agent (omnipaque) will be injected into the vein and CT will be performed to visualize the flow of contrast material through the vessels, focusing on the site of the aneurysms and/or target vessel/organ.

2. List probable clinical responses to and potential complications of the nonsurgical procedure(s).

Potential complication such as allergic reaction to contrast can be determined clinically. It occurs in rare cases. Allergic reaction can show rash, vomitting, itching, sneezing and severe response including anaphylactic shock.

Any complications will be reported to the DLAM veterinary staff, and treatment will be provided on their recommendation.

Vessel spasm or dissection. Vasodilators such as Nitroglycerin or Papaverine can be administered via intravenous injection to reduce or eliminate a vessel spasm during the procedure.

Gas Anesthetic

NOTE: Gas anesthetics like isoflurane, halothane, enflurane, and ethane must be used safely. The Off ce of Environment, Health & Safety (EH&S) requires the use of a certified fume hood or a gas anesthet c machine that contains a scavenging dev ce (e.g., anesthet c gas machine w th charcoal filter; ducted fumehood or ducted b osafety cabinet; Crump WAG System; vaporizer w th a scavenging filter, such as F-air canister) when using gas anesthetics.

1. What gas anesthetic agent(s) will be used?

- ☐ Halothane
- ☑ Isoflurane
- ☐ Other:

2. Gas anesthetic(s) will be scavenged via:

- ☐ Certified Fume Hood:
- ☑ Other: Closed system, charcoal scavenger in [redacted]

Scavenging Location

This section is empty.

Hazardous Agents

If you are planning to use rDNA, chemical or biohazardous agents (carcinogenic, teratogenic, or highly toxic substances; nanoparticles; human cell lines; or infectious agents) in live animals, you are required to provide the information about the agents below. The appropriate safety committee will review your

request directly in the application.

Agent(s) that will be used:

Agent Name	Route of Administration	Volume	Time to Euthanasia	Approval Date
Midazolam	IM	2-4 ml	7 hrs	4/14/2016
N troglycerin	IA	1-3 mL	6 hrs	4/24/2015

Principal Investigator Assurance

After you have reviewed and answered yes to the items below, please click "Save" at the bottom of the page. Please note that the PI must complete this section. To determine your eligibility to serve as Principal Investigator of a research protocol, please refer to UCLA Policy 900 (Principal Investigator Eligibility) or contact the ARC administrative office (310-206-6308). If the terms of Policy 900 are not met, faculty sponsorship or principal investigatorship by a UCLA employee with faculty appointment may be required.

Regarding policies governing animal research at UCLA:

Yes	No	
◉	○	I agree to abide by all applicable federal, state, and local laws and regulat ons and UCLA pol cies and procedures.
◉	○	I am aware that deviat ons from an approved protocol or violations of applicable pol cies, gu delines, or laws could result in immediate suspension of the protocol.
◉	○	I understand that the attending veterinarian or his/her designee must be consulted in the planning of any research or procedural changes that may cause more than momentary or slight pain or distress to the animals.
◉	○	I declare that all experiments involving live animals will be performed under my supervis on or that of another qualified scientist. All listed personnel will be trained and certified in the proper humane methods of animal care and use prior to conducting experimentation.
◉	○	I understand that emergency veterinary care will be administered to animals showing evidence of discomfort, ailment or illness.
◉	○	I declare that the information provided in this appl cation is accurate to the best of my knowledge. If this project is funded by an extramural source, I certify that this appl cation accurately reflects all currently planned procedures involving animals described in the proposal to the funding agency.
◉	○	Any modificat ons to the protocol will be subm tted to and approved by the ARC prior to initiation of such changes.
◉	○	The experimental design has been refined in order to minimize the invasiveness of the proposed procedures.
◉	○	I assure that the proposed research does not unnecessarily duplicate previous experiments.

Agreement on electronic submission:

I understand that by submitting this document that this document will be sent to appropriate members for review. I further understand that once submitted for review, this protocol cannot be modified or changed unless so requested by the ARC. In addition, once approved, all changes or modifications must be subm tted for review and approval of the ARC prior to in tiation.

Completed by: [redacted] **3/1/2019**

FS Assurance

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