



December 11, 2019

Animal and
Plant Health
Inspection
Service
Animal Care
4700 River Road
Riverdale, MD
20737

(b) (6), (b) (7)(C)

Emory University
1599 Clifton Rd NE
Atlanta, GA 30322

Dear (b) (6), (b) (7)(C)

I reviewed the request from August 12, 2019 for an exception to the regulatory requirement under Title 9 Chapter 1 Subchapter A Section 2.31(d)(1)(x), that limits an animal to one major operative procedure. As per the request, a principal investigator wishes to transfer three adult rhesus macaques that previously underwent major operative procedures (craniotomies) under protocol #201700255 that studied the thalamostriatal system of the brain, to protocol # 201900088 to study the pedunclopontine nucleus of the brain for Parkinson's Disease research. Additional information regarding this request was provided September 11, 2019 and October 31, 2019. Both protocols are under the same principal investigator and the new study will also require craniotomies.

The request for an exception is **approved from December 11, 2019 to July 17, 2022** as a Special Circumstance. These animals that underwent craniotomies under one study, will be used in a different study for which craniotomies are required, reducing the need to sacrifice additional animals to achieve the same purpose. The surgeries are to be performed under protocol #201900088 during the approval period. Emory University must reflect this exception on its Annual Reports for each year within the approval period as required under Title 9 Chapter 1 Subchapter A Section 2.36(b)(3).

Your efforts to comply with the Animal Welfare Act regulations are appreciated. Another request for an exception may be submitted to animalcare@usda.gov at the end of the approval period if necessary. The Fort Collins office can be contacted at (970) 494-7478, with any questions you may have.

Sincerely,

Dr. Betty Goldentyer
Deputy Administrator of
Animal Care

Animal Care Regional Director
Raleigh, NC Office
USDA/APHIS/AC
920 Main Campus Drive Suite 200
Raleigh, NC 27606-5210

To whom it may concern,

Emory University, Registration Number 57-R-003, is requesting an exemption to APHIS Policy 14, "Multiple Survival Surgeries" for the forbiddance of a second major survival operative procedure in a separate animal study activity. Emory's IACUC reviewed this animal study at its July 3, 2019, meeting and, after minimal modifications, approved it July 17, 2019.

The requested exemption is for the NIH (grant number) and Emory IACUC-approved research protocol, "Functional Anatomy of the Pedunculo pontine Nucleus in Monkeys" and is in accordance with the APHIS principle of Reduction of animal use. Please see below for specific research and animal use details:

The goal of the research is to develop more effective treatments for Parkinson's disease by determining the organization of anatomical connections between the basal ganglia and a caudal region of the monkey brain -- the pedunculo pontine nucleus (PPN). To achieve this goal, researchers need to introduce axonal tracers in lower regions in the brainstem known to receive inputs from the PPN. The tracers will facilitate the researchers' work 1) to identify PPN neurons that project to these regions, and 2) to determine if these regions receive direct inputs from the basal ganglia. A deeper knowledge of the system is needed 1) to understand how this connection between the basal ganglia and specific subset of PPN neurons may be involved in the normal control of motor behavior, and 2) to determine how dysfunction of this connection may contribute to the emergence and severity of specific parkinsonian motor signs.

We are requesting to include three adult rhesus macaques that, for another approved, study (b) (4) had two intracerebral injections with four to eight weeks between the procedures. These three animals are being requested for the express purpose of minimizing the number of animals used on the two terminal studies. Each of these subjects have a unique code tattooed to her chest and microchips, which serves as a permanent identifiers. The proposed third surgery to inject the tracers would be at least five months after the last surgery, involve different brain regions and neuronal networks far apart from the two previous areas, and take approximately three to four hours. The animals would be maintained for six weeks post-surgery and then euthanized to collect additional data from histopathology.

The university uses the Huron eIACUC solution to manage its animal use protocols and will apply a unique tagging system to identify this proposal. Once the tags are added to the protocol, it can be found using the unique identifier tag in a searchable query within the

software solution.

Emory personnel take measures to minimize pain and distress during all procedures, closely monitors the animals post-operative and treats with analgesics as described in the IACUC protocol and as long as determined necessary by the veterinarian. Based on previous experience, the animals recover fully from the surgery with no long-term veterinary or behavioral abnormalities. Yerkes veterinary staff will monitor the animals and provide any care needed.

The justification for the additional use of the three monkeys and, therefore, the exemption is based on:

- 1) Reducing the total number of animals used in the two studies, which is in line with the three Rs recommendation to reduce to a minimum the total number of animals used in research.
- 2) Not jeopardizing the science because the injection of tracers proposed in the present project and the resulting neuronal labeling induced by these injections will not interfere with the outcome and interpretation of postmortem data that will be collected from these animals for the previous project supported by (b) (4).
- 3) Limiting the impact to the animals by:

Targeting brain structures far away in distance, across the two studies.

Ensuring the animals have recovered from the first two surgeries (see (b) (4) prior to the additional surgery.

Monitoring the animals and providing veterinary treatment as needed. The animals' current health and behavioral status is excellent, and their current body weight is stable.

We understand and acknowledge allowance of this exemption request is specific to the details above, and we will meet all other stipulated requirements of the AWA and regulations if the USDA/APHIS approves our exemption request.

Thank you for considering our request. Please let us know if you have any questions.

Sincerely,

(b) (6), (b) (7)(C)

Interim Director of the Office of Research Administration and Institutional Official

GENERAL INFORMATION	
<p>Emory U (57-R-003) requests an exception from the regulatory requirement limiting an animal to one major operative procedure.</p> <p>A Principal Investigator wishes to transfer 3 adult rhesus macaques from one protocol that studies brain function, to a different protocol that studies brain function. Both protocols are under this Principal Investigator. Animals on the request are in good health:</p> <p>(b) (4)</p> <p>Disposition: Euthanasia at the end of the study for histopathology.</p>	<p>Point of Contact (b) (6), (b) (7)(C) Emory University 1599 Clifton Rd NE Atlanta, GA 30322 (b) (6), (b) (7)(C)</p> <p>Alternate POC (b) (6), (b) (7)(C) PhD IACUC Director Emory University 1599 Clifton Road NE Atlanta, GA 30322 Office: 404-712-9510 Email: (b) (6), (b) (7)(C)@emory.edu</p> <p>Person providing contact information: Walter Guy Wiles IV wwiles@emory.edu</p> <p>Original request received 8/ 28/2019.</p> <ul style="list-style-type: none"> Follow-up responses given 9/11/19 and 10/31/19.
DETAILS	
<p>Old study</p> <p>(b) (4) "Role of Thalamostriatal System in Cognition"</p> <p>Approved: 4/9/2017</p> <p>Expires: 4/9/2020</p> <p>This protocol is still active until 4/9/2020, but experiments covered by this protocol in two of the three monkeys are now</p> <p>(b) (4)</p>	<p>New Study</p> <p>(b) (4) "Anatomy of the Primate Pedunculopontine Nucleus (PPN)"</p> <p>Approved : 7/17/2019</p> <p>Expires: 7/17/22</p> <p>The scientific goals of this experiment do not directly relate to the previous. It is a completely different study</p> <p>The goal of this project is to develop more effective treatments for Parkinson's disease by determining the organization of the anatomical connections between the basal ganglia and the PPN which is in the caudal region of the brain. Researchers plan to place axonal tracers in the lower brainstem where known inputs from the PPN occur. These</p> <p>(b) (4)</p>

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	(b) (4)
	<p>monkeys to get the same scientific data we can collect in the current three animals used under protocol (b) (4) Using naïve animals would result in euthanasia for 6 animals instead of only 3 animals. We believe that our request is in line with the principle of Reduction of Animal Use and Refinement of Experimental Protocols into the conduct of research</p>

From: [Clarke, Carol L - APHIS](#)
To: (b) (6), (b) (7)(C)
Subject: Clarifications and additional questions
Date: Tuesday, September 24, 2019 2:15:00 PM
Attachments: [2019 MMOP Emory Clarifications and Quest.docx](#)

Dear (b) (6), (b) (7)(C):

Thank you for your response to my last set of questions. Enclosed are clarifications which should be helpful, and two additional questions necessary for our review.

Please feel free to contact me at 301 851 3724 with any questions you may have. Best regards.

Carol Clarke, DVM, DACLAM

Research Program Manager

USDA/APHIS-Animal Care

4700 River Rd Unit 84

Riverdale, MD 20737

(O) 301 851 3724

From: (b) (6), (b) (7)(C)@emory.edu]
Sent: Wednesday, September 11, 2019 5:33 PM
To: Clarke, Carol L - APHIS <carol.l.clarke@usda.gov>
Subject: Re: [External] FW: Questions from the USDA

Dear Dr. Clarke,

Please see the attached document with answers to your questions. We look forward to your decision and please don't hesitate to contact me.

Regards, (b) (6), (b) (7)(C)

(b) (6), (b) (7)(C) PhD

Interim Vice President for Research Administration

Emory University, 1599 Clifton Rd NE, 4th Floor

Atlanta, GA 30322

404-727-3889 • (b) (6), (b) (7)(C)@emory.edu

From: "Clarke, Carol L - APHIS" <carol.l.clarke@usda.gov>

Date: Friday, September 6, 2019 at 10:38 AM

To: (b) (6), (b) (7)(C)@emory.edu>

Subject: [External] FW: Questions from the USDA

Dear (b) (6), (b) (7)(C):

As per my voice mail message this morning, I received your exception request and had several questions as a result.

The E-mail containing the questions (see below) unfortunately bounced back.

Hopefully I made the appropriate correction and the message should now go through.

I am available today at (b) (6), (b) (7)(C) for discussion if you wish. Best regards.

Carol Clarke, DVM, DACLAM

Research Program Manager

USDA/APHIS-Animal Care

4700 River Rd Unit 84

Riverdale, MD 20737

(O) 301 851 3724

From: Clarke, Carol L - APHIS

Sent: Thursday, September 5, 2019 5:36 PM

To: (b) (6), (b) (7)(C) @Emory.EDU

Subject: Questions from the USDA

Dear (b) (6), (b) (7)(C)

Thank you for your request for an exception to the regulatory requirement under 9 C.F.R. §2.31(d) (1)(x) that limits an animal to one major operative procedure. Please address below so we can continue processing this request. I enclosed the request for your convenience.

1. Please provide the title and protocol numbers for the first study and the new study.
 - o It is unclear whether IACUC protocol (b) (4) refers to the first study or to the new study.
2. What are the ID numbers of the animals and how old are they?
3. Were there any other major operative procedures performed in the past for scientific reasons besides the intracerebral injections?
 - o Major operative procedure: any surgical intervention that penetrates and exposes a body cavity or any procedure which produces permanent impairment of a physical or physiological function.
4. When was the new protocol approved by the IACUC and when will it expire?
5. Will the proposed work be performed by the same investigator who conducted the previous work?
 - o Clarify whether the request is a transfer of animals from one protocol to another protocol under a different investigator.
6. Please provide more details about the intracerebral injections performed in both studies.
 - o Did the procedure require a craniotomy with opening of the dura?
7. Are there funding deadlines?

Please feel free to contact me by phone (301 851-3724) or E-mail (Carol.L.Clarke@USDA.GOV) with any questions you may have.

Best regards.

Carol Clarke, DVM, DACLAM

Research Program Manager

USDA/APHIS-Animal Care

4700 River Rd Unit 84

Riverdale, MD 20737

(O) 301 851 3724

Carol.L.Clarke@USDA.GOV

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Clarifications for your information:

1. Your request is really for an exemption to a regulation:
 - a. Title 9 Chapter 1 Section 2.31(d)(1)(x) No animal will be used in more than one major operative procedure from which it is allowed to recover unless:
 - i. (A) Justified for scientific reasons by the principal investigator in writing;
 - ii. (B) Required as routine veterinary procedure to protect the health and well-being of the animal...
 - iii. or (C) In other special circumstances as determined by the Administrator on an individual basis

The intent of Policy 14 was guidance, hence not meant to be binding. We removed all policies from our website one year ago for revision.

2. The Animal Welfare Act, Section 2143(e)(3) stresses improved methods of animal experimentation including methods which could (A) reduce or replace animal use; and (B) minimize pain and distress.
 - Note: Mitigation of pain and distress is the intent.

See Act and regulations on line: https://www.aphis.usda.gov/animal_welfare/downloads/bluebook-ac-awa.pdf

Questions

- I. Re: Protocol 201700255, "Role of Thalamostriatal System in Cognition"
 - When was this study approved?
 - Has the IACUC officially expired the protocol because of lack of funding or is it merely inactive?
 - (b) (4) the Primate Pedunculo pontine Nucleus (PPN) in essence the or is it a completely different study?
- II. What is the scientific justification for using these animals? Can naïve animals be used instead?

To: Carol Clarke, DVM, DACLAM
Research Program Manager
USDA/APHIS-Animal Care
4700 River Rd Unit 84
Riverdale, MD 20737
(O) 301 851 3724
Carol.L.Clarke@USDA.GOV

Dear Dr. Clarke,

Thank you for contacting us requesting additional information regarding our exemption request to policy 14. Our responses are below:

1. Please provide the title and protocol numbers for the first study and the new study.

(b) (4) "Role of Thalamostriatal System in Cognition"
(b) (4) "Anatomy of the Primate PPN"

2. What are the ID numbers of the animals and how old are they?

(b) (4)

3. Were there any other major operative procedures performed in the past for scientific reasons besides the intracerebral injections?

- Major operative procedure: any surgical intervention that penetrates and exposes a body cavity or any procedure which produces permanent impairment of a physical or physiological function.

No

4. When was the new protocol approved by the IACUC and when will it expire?

The IACUC full committee reviewed the new protocol July 3, 2019, and the committee approved the protocol for activation July 17, 2019. Currently, the protocol is in inactive "post-review" while we await the exemption request review. Upon approval of the exemption request, we will give the protocol the approval date and code it for expiration 3 years after approval.

5. Will the proposed work be performed by the same investigator who conducted the previous work?
- Clarify whether the request is a transfer of animals from one protocol to another protocol under a different investigator

Yes, (b) (6), (b) (7)(C) is the primary investigator for both protocols and the PI in charge of both studies.

6. Please provide more details about the intracerebral injections performed in both studies.
- Did the procedure require a craniotomy with opening of the dura?

(b) (4)

(b) (4)

(b) (4)

7. Are there funding deadlines?

The NIH grant that supported protocol (b) (4) ended July 31, 2019. The per diems of these three monkeys are currently supported by discretionary funds.

The NIH grant that supports the protocol ends July 31, 2022.

Please let us know if there are any additional questions.

Sincerely,

(b) (6), (b) (7)(C)

From: (b) (6), (b) (7)(C)@emory.edu]
Sent: Wednesday, December 4, 2019 3:36 PM
To: APHIS-AnimalCare <AnimalCare@usda.gov>
Cc: (b) (6), (b) (7)(C)@emory.edu; (b) (6), (b) (7)(C)@emory.edu>
Subject: Change in IA at Emory University: 57-R-003

Dear USDA Representative,

This email is to serve as notice that effective December 1, 2019 Dr. Robert Nobles has replaced (b) (6), (b) (7)(C) as the Institutional Official and Vice President Research Administration at Emory University.

Emory University Registration Number 57-R-003
Customer Number 896

(b) (6), (b) (7)(C) PhD, CPIA
Director, Institutional Animal Care and Use Committee (IACUC)
Phone: 404-727-9510
Email: (b) (6), (b) (7)(C)@emory.edu
Internet: <http://www.iacuc.emory.edu/>

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