



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Laboratory Animal Welfare
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FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

June 22, 2022

Re: Animal Welfare Assurance
#A3012-01 (OLAW Case 1J)

Dr. William Wasilenko
Senior Associate Dean for Research
Eastern Virginia Medical School
721 Fairfax Avenue-Fairfax
Andrews Hall, (b) (4)
Norfolk, VA 23507

Dear Dr. Wasilenko,

The Office of Laboratory Animal Welfare (OLAW) has received your June 15, 2022 email with accompanying letter from the Deputy Administrator of the United States Department of Agriculture's Animal and Plant Health Inspection Service (APHIS). In her letter, the Deputy Administrator grants the requested exception for the five specific female baboons until May 6, 2024, with certain provisions. Subsequent to the granting of the exception by the USDA, your institution is compliant with the PHS Policy on Humane Care and Use of Laboratory Animals which requires assured institutions to comply with the Animal Welfare Act.

Thank you again for your cooperation and for the transparency of your program.

Sincerely,

Brent C. Morse

Digitally signed by Brent C.
Morse -S

S

Date: 2022.06.22 10:45:01
-04'00'

Brent C. Morse, DVM

Director

Division of Compliance Oversight

Office of Laboratory Animal Welfare

cc: IACUC Contact



Animal and Plant
Health Inspection
Service

4700 River Road
Riverdale, MD 20737

June 15, 2022

William J. Wasilenko, Ph.D.
Vice Dean for Research and Institutional Official
EVMS Office of Research
735 Fairfax Avenue
Waitzer Hall, Suite 1112
Norfolk, Virginia 23507

Dear Dr. Wasilenko:

I reviewed your letter dated December 20, 2021, and subsequent letters with additional information dated January 31, 2022, and February 4, 2022, related to 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. You are making this request in order to continue the work performed under protocol #21-003 (approved 05/06/2021 and expires 05/06/2024), which will entail up to 6 caesarian sections on 5 adult female baboons (*Papio anubis*).

The subject animals are identified as numbers: 26741 (date of birth 6/1/2005), 26876 (date of birth 6/29/2005), 27320 (date of birth 10/24/2005), 07105 (date of birth 10/5/2005), and 03105 (date of birth 4/11/2005). Five of the 6 animals have already undergone at least 1 prior c-section, under protocols #15-009 (expired), #18-006 (expired) and #21-003 (current protocol). The subject animals are part of a single developmental study examining the role of estrogen (estradiol) on placental-fetal development and offspring function. (Further details of the methodology and rationale were provided in your communications noted above.)

After thorough review and consideration, the exception is **approved from June 15, 2022, to May 6, 2024**, with the following provisions that EVMS must ensure:

1. All work is performed in accordance with protocol #21-003.
2. This exception applies *only* to animals 26741, 26876, 27320, 07105 and 03105.
3. No more than 6 research-related major operative procedures are performed per animal per lifetime.
4. No animal undergoes a major operative procedure under this exception after May 6, 2024, without written approval from this office.
5. Adequate recordkeeping is maintained regarding the number of surgeries performed.
6. The IACUC evaluates animal well-being along with the effectiveness and soundness of methods and procedures, a minimum of every six months during the approval period.

Any failure to abide by the above provisions will result in the automatic withdraw of APHIS' approval of this exception. This approval is in accordance with 9 C.F.R. § 2.31(d)(1)(x)(C). If there are any questions, please contact your inspector, the Fort Collins office at (b) (6) or send inquiries to animalcare@usda.gov. Thank you.

Sincerely,

ELIZABETH
GOLDENTYER

Digitally signed by ELIZABETH
GOLDENTYER
Date: 2022.06.15 13:42:45 -04'00'

Betty Goldentyer, DVM
Deputy Administrator

An Equal Opportunity Provider and Employer

May 24, 2022

Brent C. Morse, DVM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare

Re: Animal Welfare Assurance
#A3012-01 (OLAW Case 1J)

Dear Dr. Morse,

We are responding to your request for an explanation of the circumstances surrounding this case. Below, we provide a summary of the events leading to the noncompliance citation, along with additional information about: the status of the study supported by NIH grants DK 120513 and HD 93070 and EVMS funds, the proposed study animals, and all amended actions taken by the institution. Please note that much of the information regarding this matter was included in our correspondences to the USDA.

SUMMARY OF EVENTS:

A. On September 14, 2021, EVMS received an inspection report submitted by USDA Veterinary Medical Officers (VMOs), Rachel Perez-Baum, DVM, MPH and John F. LoPinto, DVM, which included a citation related to **AWR 2.31(d)(1)(x) - Institutional Animal Care and Use Committee (IACUC)**, which states the following:

No animal will be used in more than one major operative procedure from which it is allowed to recover unless:

- (A) Justified for scientific reasons by the principal investigator in writing;**
- (B) Require as routine veterinary procedure or to protect the health or well-being of the animals as determined by the attending veterinarian; or**
- (C) In other special circumstances as determined by the Administrator on an individual basis. Written requests and supporting data should be sent to APHIS, Animal Care.**

The USDA inspection report was submitted in follow-up to a routine inspection of the EVMS animal care facility and IACUC records. Specifically, it states that at least three female baboons (i.e., ID# 26876, ID# 26741, and ID# 28768) were subjected to multiple major operative procedures on more than one IACUC-approved protocol without prior approval from the APHIS Administrator. It further states that the protocols in question (i.e., #15-009, #18-006, and #21-003) do not include scientific justification for the surgical procedures, nor has EVMS sought or received approval from the Administrator for any of the identified animals or documented procedures.

Research

735 FAIRFAX AVENUE, WAITZER HALL - SUITE 1112
NORFOLK, VA 23507

Page 1 | 6 TEL 757.446.8480
www.evms.edu

B. All multiple survival surgeries were suspended on the protocol after the citation and remain suspended as EVMS awaits a determination from the USDA regarding an exception request.

C. On September 24, 2021 EVMS requested clarification from the APHIS Animal Care regarding the need for Administrator approval for multiple major survival surgeries in this situation. No response was provided to EVMS.

D. EVMS submitted an appeal of the citation to the USDA on September 20, 2021. The USDA denied the appeal on October 19, 2021.

E. EVMS submitted a request for an exception to the APHIS Administrator on December 21, 2021 and additional information requested by the USDA on February 1, 2022 and February 2, 2022. We have not received an exception determination as of yet.

Below we provide Background about the protocol and rationale for multiple surgeries as reviewed by the IACUC, its continuing reviews, tracking, the appeals process and rationale for the exception request.

BACKGROUND AND EVMS PROJECT (PROTOCOL) OBJECTIVE: The original version of the research project in question began at EVMS in the mid-1980s and has continued, in large part, as a federally funded project to this day. Over the years, the project has been amended, as applicable, based upon research outcomes. The overall objective of each protocol referenced in the inspection report is to study the role of estrogen in pregnancy using a baboon model in which pregnant animals will be treated with estradiol (Grant HD 93070 and EVMS funds) or a specific inhibitor of estrogen synthesis alone or in combination with estrogen (Grant DK 120513 and EVMS funds). Treated/untreated animals will be delivered by cesarean section at early, mid, or late gestation and the placenta and fetal tissues will be collected and studied for aspects of biochemical/physiologic maturation. In other experiments, treated/untreated animals will be delivered near-term and neonates will be reared to adulthood. Development of vascular function (e.g., ability to control blood pressure), blood vessel flow, and glucose (sugar) regulation will also be determined as indices and/or predictions of development of diabetes. These studies serve as a model for the human and are designed to provide new information which will enhance understanding of the causes of pregnancy complications in women (e.g., preeclampsia, fetal growth retardation) and the role of estrogen in utero on programming fetal organ systems critical for development of appropriate vascular (e.g., blood pressure) and metabolic (e.g., glucose-diabetes) function in adulthood.

EVMS PROJECT (PROTOCOL) CONTINUATION AND ADMINISTRATIVE TRACKING: The objective section of each cited protocol clearly states the above-referenced objective, which supports our premise that the protocols are not multiple projects, but rather one continuous research project that has spanned for more than, but clearly over, the last six years. In keeping with the NIH Office of Laboratory Animal Welfare (OLAW) requirement for all approved lab animal research activities to undergo a complete review at least once every three years, the **project** has undergone triennial de nova reviews, with the latest reviews conducted in 2015, 2018, and 2021. The specific protocol numbers assigned after each review and IACUC approval (i.e. 15-009; 18-006; 21-003) are merely unique identifiers used administratively to document and track each newly reviewed and IACUC-approved version of the same project. Furthermore, the eighth edition of the *Guide for the Care and Use of Laboratory Animals*, states the following (p. 30): "Multiple major

surgical procedures on a single animal are acceptable only if they - (1) are included in and are (?) essential components of a single research project or protocol, and (2) are scientifically justified by the investigator." It further states (p. 30) that, "When applicable, the IO must submit a request to the USDA/APHIS and receive approval in order to allow a regulated animal to undergo multiple major survival surgical procedures in separate unrelated research protocols (USDA 1985, 1997a)." Based upon our contention that each protocol (i.e., uniquely identified protocol) is an IACUC-approved continuation of the same over-arching research project, we maintain that multiple major survival surgeries were not performed on animals assigned to separate unrelated protocols. Rather, we contend that the surgeries were performed on animals assigned to a single research project, which, by definition makes them acceptable and scientifically justified. To that end, prior approval from the USDA/APHIS to perform the surgeries was not warranted.

RATIONALE AND CONSIDERATIONS FOR AN APPEAL AND SUBSEQUENT EXCEPTION REQUEST : On September 20, 2021, EVMS submitted an appeals request to the USDA containing the following information and considerations:

A. We respectfully request USDA reconsideration and removal of the citation because we believe it is incorrect with respect to AWR 2.31(d)(1)(x)(A). The IACUC surgery attachment (**Attachment E: Animal Surgery**) included with each protocol outlines the proposed surgical procedures, explains how the surgeries are related, and justifies the need for more than one surgery per animal. Additionally, it clearly states the number of surgeries each animal will undergo while assigned to the project (protocol), identifies animals that have undergone prior surgeries under a previous unique numerical identifier, and it justifies the need to reuse those animals in the current surgical protocol (i.e., under the current unique identifier). In particular and for example, the current protocol (#21-003) states: that the protocol is designed to elucidate the role of estrogen on placental fetal development and the function and impact on adrenocortical self-sufficiency in the perinatal period and metabolic and vascular function in adulthood. Thus, surgeries are related to each other both by development and by estrogen. We study the animal at discrete times in control (no treatment) and treated with Letrozole with or without estradiol-benzoate at early and late gestation. Thus, each animal essentially serves as its own control. The major survival surgery to be performed is a cesarean section. Each animal may undergo up to six (6) major survival surgeries. However, while six is the optimal number of procedures to achieve statistically valid data, we work closely with the Attending Veterinarian (AV) who ensures that animals are healthy and have no medical and/or behavioral complications (e.g., excessive adhesions, uterine windows, endometriosis, etc.) that would not be compatible with performing an additional surgery. Animals were not used in an unrelated protocol.

This protocol is the 3-year continuation of IACUC #18-006. The animals in this protocol were used in the prior approved IACUC protocol as subjects assigned to the same continuous research project. Multiple use of the same baboon reduces the total number of animals required to conduct the study and still permit collection of statistically valid data. Thus, we study the role of estrogen in the same baboon (i.e., experiments are interrelated/integrated) during control periods (e.g., on days 60 and 110 of gestation). One animal rather than 5 animals are studied. Multiple pregnancies also mimic the situation in humans. Recent (2020) CDC data indicate that 31.8% of all pregnancies use cesarean section, with 21.9/100 live births using this as a primary delivery method.

NOTE: Redacted copies of the three protocols were provided to Dr. Perez-Baum during the September 2021 on-site inspection. She uploaded the copies to the USDA portal so the documents are available for the Appeals Committee to reference during its deliberations.

B. Additionally, we request reconsideration and removal of the citation because we believe it is inconsistent with the letter and spirit of AWR 2.31(d)(1)(x)(C) and does not take into consideration historical context/content and professional guidance provided by three former VMOs. As previously stated, the protocol number assigned following the triennial review of approved activities is a unique identifier used for administrative purposes only to document and track each newly reviewed and IACUC-approved version of the same project. In light of that information and given our interpretation of the regulation, we maintain that the animals identified in the report have not undergone multiple major operative procedures in more than one IACUC-approved protocol, but rather the animals were assigned to and surgically manipulated under the same project tracked using different numerical identifiers.

The various protocols related to the parent (umbrella) project and the veterinary records for the animals assigned to that project have undergone annual review by the USDA since the project began, as required by federal regulation. Additionally, the IACUC policy, which allows for a non-human primate (NHP) to experience multiple major survival surgeries over its lifetime, when scientifically justified, has been reviewed numerous times by the USDA, along with our accrediting body, AAALAC International. In October 2000, both the USDA and AAALAC International recommended that the Committee revise its multiple major survival surgery (MMSS) policy with respect to a defined end-point based upon age, lab values, number of procedures, physical exam, and/or behavioral changes; types of allowable surgeries; and animal health/well-being and assessment of scientific justification prior to subsequent surgeries. The IACUC followed the recommendation of both agencies and, on March 6, 2001, the policy was revised accordingly. The current policy allows for up to six survival surgeries when appropriately justified. Additionally, on February 4, 2008, AAALAC International asked the IACUC to revisit and reaffirm its policy on MMSS, particularly in light of the six-surgery allowance. The policy was reviewed by the IACUC at its February 7, 2008 meeting, at which time the Committee fully supported and endorsed the policy as written.

During the January 24, 2008 USDA routine inspection (records review only), the VMO confirmed that she had reviewed the MMSS policy many times over the years, that the policy has been accepted by the USDA, and that an exemption from the USDA is not required each time a multiple major survival surgery is performed. That statement by the VMO is documented in the February 7, 2008 minutes. When the VMO returned on April 8, 2008 to conduct a routine inspection of the animal care facility, the MMSS policy was discussed once again. The VMO stated that when the policy was first presented to the USDA, the agency determined that an exemption/exception was not needed; therefore, the current policy is acceptable. The VMO further stated that she would inquire about the agency's current ruling on the policy and would inform the institution of a different, more recent determination, if applicable. No updated determination by the USDA was provided. The actions of the IACUC in response to the USDA and AAALAC International recommendations are recorded in the July 30, 2008 IACUC annual report to the Dean.

After the original VMO retired in November 2014, the MMSS policy was reviewed and endorsed by two subsequent VMOs. Each concurred with the assessment and guidance of the original VMO concerning the MMSS policy and USDA Administrator approval.

The following items were attached in support of the USDA appeals request and may be provided to OLAW upon your request:

1. USDA letter to EVMS dated October 9, 2000
2. EVMS response to AAALAC International dated October 20, 2000
3. EVMS policy, *Multiple Major Survival Surgery in Experimental Animals*, Effective Date: March 6, 2001
4. February 7, 2008 IACUC-approved minutes - MMSS policy reaffirmation excerpt
5. April 8, 2008 USDA Inspection Exit Briefing Notes - MMSS policy and Administrator approval discussion excerpt
6. July 30, 2008 IACUC Annual Report to the Dean - MMSS policy discussion excerpt
7. Current EVMS policy, *Multiple Major Survival Surgery in Experimental Animals*, Latest Revision: March 2, 2017
8. Add 2 additional letters in response to USDA##??

Based upon our understanding/interpretation of the AWR, and in compliance with the professional guidance of multiple previous VMOs, we propose that this information supports our premise that (1) the animals in question did not undergo MMSS under more than one IACUC-approved protocol, (2) sufficient scientific justification was provided by the principal investigator (PI) to support multiple procedures on a given animal, and (3) a request for approval for the APHIS Administrator was not required. We further submit that the EVMS IACUC has made concerted good faith efforts to regularly review and revise the MMSS policy, as needed. Additionally, as required by federal regulation, continuing reviews of the IACUC-approved activities are performed not less than annually and a complete de novo review of the activities is completed triennially. We are happy to report that no animal welfare issues have been reported following the surgeries performed to date under #15-009, #18-006, or #21-003.

We attribute the success of the surgeries and the overall well-being of the animals to excellent care and management provided by the investigative and veterinary care staff and careful coordinated oversight provided by the IACUC.

As noted above, since September 14, 2021, all multiple major operative procedures approved under #21-003 have been suspended. The PI has been informed that multiple surgeries may not resume until clear guidance from the USDA has been provided. A request for clarification on whether Administrator approval is required was submitted to APHIS Animal Care under separate cover on September 24, 2022.

APPEALS PROCESS DETERMINATION AND SUBSEQUENT ACTIONS:

On October 19, 2021, EVMS learned that the appeal request was denied. EVMS therefore requested an exception for future multiple major survival surgeries on the protocol. MMSS exception was submitted on December 21, 2021. There were two additional requests from the USDA for supplemental information regarding the MMSS exception. We responded to those requests on February 1, 2021 and February 2, 2021. To date we have not received further communication from the USDA. Dr. William J.

Wasilenko, Institutional Official (IO) and, Dr. Mario Rodriguez, AV have sent several follow-up emails to our USDA contact for information on when a response regarding the exception request may be forthcoming. Once we receive the final communication from the USDA regarding the requested exception, the institution will follow the stated guidance and inform OLAW of the decision by USDA.

Please let us know if you have additional questions or require more information regarding the matters with protocol #21-003.

Sincerely,

(b) (6)

Frank A. Lattanzio, Ph.D., Chair
Institutional Animal Care and Use Committee

(b) (6)

William J. Wasilenko, Ph.D.
Vice Dean for Research
Institutional Official

Morse, Brent (NIH/OD) [E]

From: Morse, Brent (NIH/OD) [E]
Sent: Thursday, June 16, 2022 7:32 AM
To: Wasilenko, William J.
Cc: (b) (6) Lattanzio, Frank A.; (b) (6)
Subject: RE: [EXTERNAL] RE: Emailing: Wasilenko EVA 3012-1J

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Wasilenko,

Thank you for providing this important information. We will be sending you an official communication regarding this case very soon. (b) (6)

Best regards, Brent Morse

P.S. Please send an official notification of change of Institutional Official to OLAW's Division of Assurances (OLAWDOA@od.nih.gov) when the transition occurs. Thank you.

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: Wasilenko, William J. <WasileWJ@EVMS.EDU>
Sent: Wednesday, June 15, 2022 7:13 PM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>
Cc: (b) (6) (b) (6) Lattanzio, Frank A. <lattanfa@EVMS.EDU>; (b) (6)
Subject: Re: [EXTERNAL] RE: Emailing: Wasilenko EVA 3012-1J

Hello Dr. Morse

As a follow up to our letter in late May, EVMS wishes to share with you the recent determination from the USDA about multiple survival surgeries in our baboon study and case number A3012-1J.

The EVMS IACUC will review and plan to implement these USDA requirements for this study going forward.

Please feel free to contact me with questions, concerns or recommendations.

Best regards

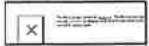
Bill Wasilenko

William J. Wasilenko, PhD
Vice Dean for Research

Eastern Virginia Medical School | Office of Research

(b) (4) *Waitzer Hall | 735 Fairfax Ave. | Norfolk VA 23507 |*

(b) (6) * wasilewj@evms.edu



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On May 25, 2022, at 7:51 AM, Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov> wrote:

Thank you for providing this requested information, Dr. Wasilenko. I will review your letter and send an official response soon.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
 Director, Division of Compliance Oversight
 Office of Laboratory Animal Welfare
 National Institutes of Health

From: Wasilenko, William J. <WasileWJ@EVMS.EDU>

Sent: Tuesday, May 24, 2022 5:09 PM

To: Ward, Joan (NIH/OD) [E] <wardjoa@od.nih.gov>

Cc: (b) (6) Lattanzio, Frank A.
 <lattanfa@EVMS.EDU>

Subject: [EXTERNAL] Re: Emailing: Wasilenko EVA 3012-1J

Dear Ms. Ward

As requested below, please find the EVMS response to Dr. Morse's request for information concerning OLAW case A3012-1J. We are happy to provide additional information to OLAW.

Sincerely,

Dr. Wasilenko (IO)

William J. Wasilenko, PhD
Vice Dean for Research

Eastern Virginia Medical School | Office of Research

(b) (4) Waitzer Hall | 735 Fairfax Ave. | Norfolk VA 23507 |
(b) (6) * wasilewj@evms.edu



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On Apr 13, 2022, at 7:51 AM, Wasilenko, William J. <WasileWJ@evms.edu> wrote:

Dear Ms. Ward

We have received your correspondence from Dr. Morse and will provide the requested information concerning the USDA report.

Thank you

Dr. Wasilenko

William J. Wasilenko, PhD
Vice Dean for Research

Eastern Virginia Medical School | Office of Research |
(b) (4) Waitzer Hall | 735 Fairfax Ave. | Norfolk VA 23507 |
(b) (6) | wasilewj@evms.edu

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-----Original Message-----

From: Ward, Joan (NIH/OD) [E] <wardjoa@od.nih.gov>

Sent: Wednesday, April 13, 2022 7:30 AM

To: Wasilenko, William J. <WasileWJ@EVMS.EDU>

Cc: (b) (6)

Subject: [EXTERNAL] FW: Emailing: Wasilenko EVA 3012-1J

Dear Dr. Wasilenko,

Attached please find Dr. Morse's initial response to OLAW Case A3012-1J.

If you have any questions, feel free to contact us by phone or by e-mail.

Best Regards,
Joan

Joan Ward
Program Specialist
Office of Laboratory Animal Welfare
National Institutes of Health
6700B Rockledge Dr., Suite 2500
Bethesda, MD 20892

301-496-7163
wardjoa@od.nih.gov

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DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

FOR US POSTAL SERVICE DELIVERY:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500, MSC 6910
Bethesda, Maryland 20892-6910
Home Page: <http://grants.nih.gov/grants/olaw/olaw.htm>

FOR EXPRESS MAIL:

Office of Laboratory Animal Welfare
6700B Rockledge Drive, Suite 2500
Bethesda, Maryland 20817
Telephone: (301) 496-7163
Facsimile: (301) 480-3387

April 13, 2022

Re: Animal Welfare Assurance
#A3012-01 (OLAW Case 1J)

Dr. William Wasilenko
Senior Associate Dean for Research
Eastern Virginia Medical School
721 Fairfax Avenue-Fairfax
Andrews Hall, (b) (4)
Norfolk, VA 23507

Dear Dr. Wasilenko,

The Office of Laboratory Animal Welfare (OLAW) has received information from the United States Department of Agriculture (USDA) relating to a study at your institution funded by the Public Health Service. The USDA recently determined that at least one animal on this study, a female baboon, underwent more than one major surgical procedure for experimental purposes without appropriate review and approval from the USDA Deputy Administrator for Animal Care. If so, this is also a noncompliance with the PHS Policy on Humane Care and Use of Laboratory Animals which requires assured institutions to comply with the Animal Welfare Act.

As authorized under section V. A. 4. of the PHS Policy, and as referenced in your Animal Welfare Assurance for Humane Care and Use of Laboratory Animals, OLAW is requesting that your institution provide an explanation of the circumstances surrounding this issue. Specifically, to prevent duplication of effort on the part of your institution, please instruct the IACUC, avoiding any conflict of interest, to prepare a brief summary of the events leading to the noncompliance, and provide any further information regarding the status of the study, the proposed study animals, and all corrective/preventive actions. Please, also provide the full PHS grant number in your reply.

We appreciate your cooperation and ask that you please provide the requested information **by May 27, 2022**. Please contact me if I can be of assistance.

Sincerely,

Brent C. Morse - Digitally signed by Brent C.
Morse -S
Date: 2022.04.13 07:16:09 -04'00'

S

Brent C. Morse, DVM
Director
Division of Compliance Oversight
Office of Laboratory Animal Welfare

cc: IACUC Contact

A3012-1J

Morse, Brent (NIH/OD) [E]

From: Morse, Brent (NIH/OD) [E]
Sent: Thursday, February 24, 2022 2:08 PM
To: Clarke, Carol L - MRP-APHIS; Tubbs, Jai (NIH/OD) [E]
Cc: Bassage, Lance H - MRP-APHIS; Maginnis, Gwendalyn M - MRP-APHIS; Miller, Dana - MRP-APHIS; PerezBaum, Rachel - MRP-APHIS
Subject: RE: Concerns about an assured institution

Thank you for providing this information , Dr. Clarke. We will review the documents and investigate any potential violation of the PHS Policy which, as you know, requires compliance with applicable USDA regulations. We will keep the USDA informed of the progress of OLAW's investigation.

Best regards, Brent Morse

Brent C. Morse, DVM, DACLAM
Director, Division of Compliance Oversight
Office of Laboratory Animal Welfare
National Institutes of Health

From: Clarke, Carol L - MRP-APHIS <carol.l.clarke@usda.gov>
Sent: Thursday, February 24, 2022 1:47 PM
To: Morse, Brent (NIH/OD) [E] <morseb@mail.nih.gov>; Tubbs, Jai (NIH/OD) [E] <jacquelyn.tubbs@nih.gov>
Cc: Bassage, Lance H - MRP-APHIS <lance.h.bassage@usda.gov>; Maginnis, Gwendalyn M - MRP-APHIS <gwendalyn.m.maginnis@usda.gov>; Miller, Dana - MRP-APHIS <dana.miller2@usda.gov>; PerezBaum, Rachel - MRP-APHIS <Rachel.PerezBaum2@usda.gov>
Subject: [EXTERNAL] Concerns about an assured institution

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and are confident the content is safe.

Dear Dr. Morse and Dr. Tubbs:

My purpose in contacting you is to inform you of a noncompliance at Eastern Virginia Medical School D-16-00007, and A-3022-01 that OLAW may wish to look into. The study in question raises concerns about animal health and well-being.

In September 2021, our inspector found evidence that multiple major operative procedures were occurring on transferred animals without obtaining approval from the DA of Animal Care to conduct this work. [See enclosed inspection report].

The school responded on 12/21/21, by submitting an exception request for approval. They want to perform up to 6 successive C-sections on 5 baboons to study estradiol events on fetus and the dam. The exception is only needed for 3 animals that were transferred from other studies. Of those 3, two already had 3 C-sections.

Despite responses to our questions, we are still unclear why 6 C-sections are necessary and how an animal that undergoes C-sections annually can serve as its 'own control' as they state. The study design and scientific justification are hard to follow. We are very concerned about pain/distress and whether 6 C-sections on one animals are adequately scientifically justified.

I was reminded during our deliberations that the work is PHS funded, hence I am bringing OLAW into the loop before going any further.

The rest of the attachments are pdfs of the request (12.21.21) and responses to my questions. I am on leave March 3-9th and my last official day is March 10th. Let me know whether OLAW will pursue any actions. Best regards.

Carol Clarke, DVM, DACLAM
Senior Staff Officer (Laboratory Animals)
APHIS-Animal Care-National Policy Staff
4700 River Rd
Riverdale, MD 20737

(b) (4)



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Inspection Report

EASTERN VIRGINIA MEDICAL SCHOOL
358 MOWBRAY ARCH, PO BOX 1980
NORFOLK, VA 23501

Customer ID: 497

Certificate: 52-R-0003

Site: 001

EASTERN VIRGINIA MEDICAL
SCHOOL

Type: ROUTINE INSPECTION

Date: 14-SEP-2021

2.31(d)(1)(x) Critical

Institutional Animal Care and Use Committee (IACUC).

At least three female baboons have undergone multiple major operative procedures on more than one IACUC approved protocol without prior approval from the APHIS Administrator. Protocol 21-003 involves a major operative procedure from which animals are recovered. Medical records and study records indicate that, three adult female baboons (ID #: 26876, 26741, and 28768) have each undergone major operative surgeries on prior protocols as well as the current protocol.

1. Female Baboon ID# 26876: Underwent 3 cesarian sections: twice on protocol #18-006 on 4/18/2019 and 1/10/2020, and once on protocol #21-003 on 6/17/2021.

2. Female Baboon ID# 26741: Underwent 3 cesarian sections: twice on protocol #15-009 on 9/20/2016 and 8/28/2017, and once on protocol #18-006 on 3/20/2020.

3. Female Baboon ID# 28768: Underwent 3 cesarian sections: once on protocol #15-009 on 3/27/2017, and twice on protocol #18-006 on 7/22/2019 and 4/15/2021.

Protocols 15-009, 18-006, and 21-003 are a continuation of the same study with identical study objectives. The protocols indicate animals will be undergoing multiple major surgeries but do not provide a scientific justification nor have approval from the Administrator. These protocols, which have each been reviewed and approved by the IACUC, have spanned over 6 years. According to the facility, due to the multiple surgeries performed, the IACUC created a policy to limit the

Prepared By: RACHEL PEREZ-BAUM

USDA, APHIS, Animal Care

Date:

15-SEP-2021

Title: VETERINARY MEDICAL
OFFICER

Received by Title: IACUC Representative

Date:

15-SEP-2021



Inspection Report

number of major operative procedures an individual animal can undergo to a maximum of six in the animal's life. The facility has not sought or received approval from the Administrator for any of the animals that have undergone multiple major operative procedures on any of the protocols.

Animals that undergo major operative procedures and are recovered are subjected to stress, pain and discomfort.

Correct by the end of 9/15/2021 by not allowing any animal to undergo more than one major operative procedure from which the animal recovers, without a justified scientific reason by the principal investigator and/or receiving prior approval from the USDA Administrator.

3.125(a) Critical Facilities, general.

One female chinchilla (2689L) was injured by a plastic hut that was used in the primary enclosure. Records from Protocol 19-015 indicated that this animal had a toe caught in the hut on 03/18/2020. This was observed on the same day a protocol procedure was performed. The animal was treated with pain relief in accordance with the protocol and referred to veterinary staff for evaluation and treatment. It was diagnosed with a dislocated and/or fractured toe and ultimately lost part of the digit.

Injuries such as fractures or loss of a digit are painful and cause unnecessary discomfort.

Following this incident, the facility changed the type of huts used for all chinchillas to an alternate style. There have been no additional occurrences since that time. Correct by 9/15/2021 by ensuring that all facilities housing animals are maintained appropriately and protect the animals from injury.

This inspection was conducted with the Attending Veterinarian, IACUC administrator, and Project Manager. The exit interview was conducted with the Institutional Official, IACUC Chair, IACUC administrator, and Project Manager.

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Date:
15-SEP-2021

Title: VETERINARY MEDICAL
OFFICER

Received by Title: IACUC Representative

Date:
15-SEP-2021



Inspection Report

Additional Inspectors:

JOHN LOPINTO, VETERINARY MEDICAL OFFICER

Prepared By: RACHEL PEREZ-BAUM

USDA, APHIS, Animal Care

Date:
15-SEP-2021

Title: VETERINARY MEDICAL
OFFICER

Received by Title: IACUC Representative

Date:
15-SEP-2021



United States Department of Agriculture
Animal and Plant Health Inspection Service

Customer: 497
Inspection Date: 14-Sep-2021

Species Inspected

Cust No	Cert No	Site	Site Name	Inspection
497	52-R-0003	001	EASTERN VIRGINIA MEDICAL SCHOOL	14-SEP-2021

Count	Scientific Name	Common Name
000010	<i>Macaca fascicularis</i>	CRAB-EATING MACAQUE / CYNOMOLGUS MONKEY
000001	<i>Oryctolagus cuniculus</i>	DOMESTIC RABBIT / EUROPEAN RABBIT
000016	<i>Papio anubis</i>	OLIVE BABOON
000007	<i>Macaca mulatta</i>	RHESUS MACAQUE
000028	<i>Chinchilla lanigera</i>	CHINCHILLA
000062	Total	

December 20, 2021

USDA Animal and Plant Health Inspection Service (APHIS)
Animal Care
4700 River Road, Unit 84
Riverdale, MD 20737-1234
Email: animalcare@usda.gov

Dear Administrator:

RE: Eastern Virginia Medical School (EVMS), Norfolk, Virginia
Customer ID: 497
Certificate Number: 52-R-0003
Request for a Multiple Major Survival Surgery (MMSS) Exemption for EVMS Protocol #21-003
Species: Baboon (*Papio anubis*)

In keeping with AWR §2.31(d)(1)(x)(A)(B)(C) and on behalf of the EVMS Institutional Animal Care and Use Committee (IACUC), I submit this request for a USDA-granted exemption to allow animals to be transferred to EVMS Protocol #21-003 from the same project's previous protocol # 18-006. The 5 females for which a transfer is requested had surgeries under the previous protocol number but the same project. As described below we request that these animals for scientific reasons undergo additional major operative procedure(s) (namely a cesarean section) from which they are allowed to recover. In addition to these specific 5 female baboons, all females in this project will likely spend more than 3 years in the facility/program and will therefore require transfer from previous protocol numbers after renewal. Accordingly, I also request consideration for approval of the exception for these 5 and future females. All such animals will be identified to the USDA once enrolled into the program. As outlined in **USDA Policy #14**, entitled *Major Survival Surgery*, the following information is offered in support of the request:

USDA Policy #14 Requirement	EVMS Response/Supporting Information
1. Outline of the research proposal	<p>The protocol is designed to elucidate the role of estrogen on placental fetal development and function and impact on metabolic and vascular function in adulthood.</p> <p>A: Study Design</p> <p>This is a developmental study to examine the role of estradiol throughout the course of pregnancy on placental-fetal development and impact on physiologic function in male and female offspring. Pregnancy in baboons as in humans is characterized by 3 periods (trimesters) in which:</p>

- **Different overlapping processes occur in the placenta-** e.g. placental cell migration to uterine spiral arteries (day 1-60); placental angiogenesis (day 60-term); placental structural organization/modifications (days 120-term);
- **Different overlapping processes occur in the fetus -** e.g. cellular differentiation (days 1-60); cellular hyperplasia (days 60-120); cellular hypertrophy and gene silencing/programming (days 120-term);

Accordingly, we obtain placenta and fetal tissues (fetus) on day 60, days 100-120, and days 165-175 of gestation as well as deliver and study offspring born to untreated animals to understand the normal developmental pattern of intrauterine tissue development and offspring function and relationship to endogenous estradiol levels.

B: To test the hypothesis that it is estradiol that controls these developmental changes we have 4 treatment groups:

1. Maternal treatment with exogenous estradiol on days 25-59 of gestation to pharmacologically elevate estradiol to levels normally seen after the first trimester
2. Maternal treatment with the aromatase inhibitor letrozole to reduce estradiol to very low levels and thus prevent exposure of fetus and placenta to high levels of estradiol
3. Maternal treatment with letrozole plus estradiol to restore exposure of placenta and fetus to estradiol (and thus assess the role of estradiol per se)
4. Administration of estradiol to fetuses of letrozole treated mothers on day 165 of gestation and delivery of fetus 6 or 24 hours later to examine the mechanisms of estradiol action in the fetus.

RESEARCH DESIGN: To accomplish our goals and study the role of estrogen in pregnancy, pregnant baboons will be treated with estradiol or a specific inhibitor of estrogen synthesis alone or in combination with estrogen. Treated/untreated animals will be delivered by cesarean section at early, mid, or late gestation and the placenta and fetal tissues will be collected and studied for aspects of biochemical/physiologic maturation. In other experiments, treated/untreated animals will be delivered near term and neonates will be reared to adulthood. In these animals development of vascular function (e.g., ability to control blood pressure), blood vessel flow, and glucose (sugar) regulation will also be determined as indexes and/or predictions of development of diabetes.

These studies serve as a model for the human and are designed to provide new information which will enhance our understanding of the causes of pregnancy complications in women (e.g., preeclampsia, fetal growth retardation, and prematurity per se) and the role of hormones (i.e. estradiol) in utero on programming fetal organ systems critical for development of appropriate vascular (e.g., blood pressure) and metabolic (e.g., glucose-diabetes) function in adulthood.

The EVMS IACUC assigns a unique number to each approved protocol.

2. Research
proposal unique
identifier

Research
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3. Species and approximate number of animals involved in the exemption request	Papio anubis/cynocephalus (Baboons) – currently 5 specific females fall into the category of multiple survival procedures but we are requesting that the project reviewed for more animals in the future because, as outlined below, the project aims and the design surpass the three-year renewal period for each protocol. The IACUC approved protocol (#21-003) is approved for 35 adult baboon females under USDA Pain Code Level D that will undergo multiple surgeries where they will be allowed to recover.
4. Method to permanently identify the individual animals involved	Each animal arrives at EVMS with a tattoo of the animal's unique identifier (a unique combination of letters and/or numbers). Experienced technicians tattoo animals born at EVMS in-house. As necessary, tattoos are re-inked at EVMS to maintain legibility.
5. Time frame for the proposed exempt procedure	Proposed exempt procedures will take place within a 3 to 9 year period of the IACUC-approved protocols.
6. Number of major operative procedures to be performed on a given animal, the frequency of such procedures, and the period of time between each major operative procedure	Our IACUC has approved conduct of up to 6 C-sections for each animal in this project. After each C-section, the females are allowed at least 4 months to recover before attempting a new breeding cycle and, depending on the research treatment, a new experiment/and cesarean section can occur at 2, 4 or 6 months of gestation which is 6-12 months after the last cesarean section. Animals may also be allowed to deliver and rear the offspring who are weaned at 8 -12 months of age. This means that there will be a minimum period of 6 months but up to 2 years, between experiments on any one female baboon. Also, the afore-mentioned time frames are best case scenarios and do not consider that most females do not get pregnant immediately and thus require multiple breeding attempts. Most importantly, any animal that shows signs of any pain, distress, or disease gets a clinical evaluation and appropriate treatment as designed by our AV. Such an animal would not be allowed to breed until completely healed, and if not healthy/fully healed is excluded from the protocol by the AV.
7. Measures taken to ensure that pain/distress are minimized	<ul style="list-style-type: none"> a. Positive reinforcement training is used to encourage animals to cooperate with research tasks. Examples include gradual acclimation to the cage squeeze mechanism and to the temporary discomfort associated with injections. Staff members are trained to use a pleasant tone of voice, perform tasks as quietly as practical, and approach animals with relaxed facial expressions and body postures. Rewards typically include a small food item or prompt access to the social pair. b. Animals are housed in compatible social pairs or small groups, with appropriate enrichments (e.g., novel foods, toys, audio/visual stimulation) to reduce stress and enhance well-being. c. Surgical procedures are performed after the animal has achieved a surgical plane of anesthesia (isoflurane inhaled in oxygen). This surgical plane of anesthesia is maintained throughout the surgical procedure and an experienced anesthetist constantly monitors animal's vitals. d. Post-surgical pain is controlled by a non-steroidal anti-inflammatory drug (NSAID), and/or a combination of opioid and NSAID. These medications are administered using therapeutic doses

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established for this species and administered based on the weight of the individual animal. Currently, Flunixin meglumine (2mg/kg BID intramuscularly) and Ketoprofen (2-5 mg/kg; once daily as recommended by the Attending Veterinarian) are approved and used.

- e. Sustained release medications are used when available to minimize the total number of injections given. Sustained release buprenorphine approved dosage is 0.1-0.3 mg/kg in a single administration.
- f. Trained staff members monitor post-surgical recovery. All personnel have been trained to identify indications of pain and/or distress, including failure to resume eating and drinking, failure to produce normal amounts of urine and feces, limited movement around the cage, hunched posture, swelling/redness at the incision site, and guarding of the incision area. If signs of pain are noted, the Attending Veterinarian is alerted and appropriate treatment provided, as needed.
- g. Females on this project are breed in-house to minimize any adverse effects of transportation stress.
- h. Females on this project are allowed a long acclimation period to minimize the effect stress can have on the reproductive physiology of the animal.

8. Complete scientific justification for the Exemption. Cost is not an acceptable justification.

Rationale for multiple survival surgeries and movement of animals between 3 - year protocols.

Baboons do not move between the 4 treatment groups, as these 4 treatment groups are part of a single developmental study in which we examine the role of estrogen (estradiol) on placental fetal development and offspring function.

It is important to prove that the developmental changes detected in our group of untreated animals and the changes noted following various treatments are actually occurring in any one animal (fetus or offspring). Thus it is critical to study the animals at multiple times during gestation and/or after proposed treatments (i.e. multiple surgeries/experimental treatments).

We do recognize there must be limits on the number of pregnancies and surgical cesarean sections any one animal should undergo and thus we cannot perform each and every proposed treatment in any one animal. The IACUC has set the limits based on the experience of our AV and investigators over the decades that we have worked successfully with baboons. Accordingly, we randomly assign animals to treatment groups with the goal of not repeating these unnecessarily unless necessitated by outcomes such as fetal gender or unexpected demise of fetus/offspring.

Studies in humans examine tissues collected at term or at time of elective cesarean section in otherwise healthy women and at time of delivery in women with recurring spontaneous abortion (early gestation), preeclampsia or fetal growth restriction (sometime between weeks 27-37 of gestation). Unfortunately, while useful and important information is collected, these types of unidimensional studies do not prove cause:effect and thus we cannot and do not know whether changes are simply the result and not the cause of a disease in the mother. Moreover, we cannot do any major experimental manipulations/treatments in humans to test cause:effect.

Thus, to do similar studies in the baboon, i.e. study them once and/or limit experimental treatment within acceptable reason, would almost be the same as that done in humans and a reason not to use the baboon.

	<p>Accordingly, because we study animals at multiple times and after treatment, we obtain and continue to obtain a significant amount of data on each baboon during each pregnancy. Such information is not only important statistically, but it allows us to make more definitive conclusions about the role of estrogen on fetal placental development and offspring function.</p> <p>As you can deduce from the information provided, it is impossible to collect all the vital information we seek in a 3 year period. This is especially true when we consider that the time period between procedures can be up to 1 or 2 years as it is important to allow females to fully recover and acclimate before the next first breeding attempt.</p> <p>It is also important to recognize that animals including nonhuman primates (baboons) that are stressed either emotionally or physically, are typically infertile (do not get pregnant) due to inability to ovulate and/or implant. Since we have maintained health and breeding animals for decades, that is obviously not the situation with animals in our program.</p>
9. Assurance that all other stipulated requirements of the AWA and regulations will be met in consideration of this exemption	<p>The EVMS IACUC asserts that it will meet all stipulated requirements delineated in the AWR with respect to animal activities, the functional role of the IACUC, and as an agent of the research facility, which necessarily asserts its compliance with considerations related to this exemption request.</p>
10. Assurance that the facility's IACUC has approved the exemption	<p>Following initial IACUC approval, all protocols undergo continuing review by the IACUC within 365 days of the first year and second year anniversaries, respectively. All protocols expire at the end of the third year, and a <i>de novo</i> review of the protocol application is required to continue the protocol beyond the 3-year expiration date.</p> <p>The EVMS IACUC certifies the following:</p> <p>IACUC #18-006 was reviewed and approved by the IACUC, at which time multiple survival surgeries on one animal was approved. The <i>de novo</i> renewal of that protocol and current protocol of the same project (#21-003) was reviewed and approved also allowing multiple revival surgeries on May 6, 2021. In particular, each continuing review included a written report submitted by the PI to document the following protocol-specific information, as applicable: 1) the total number of major survival surgeries performed per reporting period, 2) the number of animals that have undergone more than one major survival surgery per reporting period, 3) the animals that have undergone six major survival surgeries to date and the intended final disposition of those animals, and 4) any surgical complications experienced during the reporting period, along with the outcome of the individual animal(s) affected. Documentation of each IACUC review/approval is maintained in writing and electronically.</p>

Thank you for your timely consideration of this request. Please feel free to contact me directly if additional information is required.

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Sincerely,

(b) (6)

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wasilewj@evms.edu

WJW/cbh

cc: Principal Investigator

Rachel Pérez-Baum, DVM, MPH
USDA Veterinary Medical Officer
APHIS Inspection Service/Animal Care
rachel.perezbaum2@usda.gov

January 31, 2022

USDA Animal and Plant Health Inspection Service (APHIS)
Carol Clarke, DVM, DACLAM
4700 River Road, Unit 84
Riverdale, MD 20737-1234
Email: carol.l.clarke@usda.gov

Dear Dr. Clarke:

RE: Eastern Virginia Medical School (EVMS), Norfolk, Virginia
Customer ID: 497
Certificate Number: 52-R-0003
Request for a Multiple Major Survival Surgery (MMSS) Exemption for EVMS Protocol #21-003
Species: Baboon (*Papio anubis*)

In keeping with AWR §2.31(d)(1)(x)(A)(B)(C) and on behalf of the EVMS Institutional Animal Care and Use Committee (IACUC), I submit the following information in response to the request for additional information:

EVMS Response/Supporting Information	
1. Name, phone number, and Email of primary and secondary persons to discuss request	<p>a. Dr. William Wasilenko, (b) (6) wasilewj@evms.edu</p> <p>b. Dr. Mario Rodriguez, (b) (6) rodrigm@evms.edu</p>
2. Number of female baboons involved in the exception	We are requesting N=5.
3. Identification number and age of each animal	<p>The five (5) adult females for which we are requesting exemptions:</p> <ul style="list-style-type: none"> • 26741 – Date of Birth 6/1/2005 • 26876 – Date of Birth 6/29/2005 • 27320 – Date of Birth 10/24/2005 • 07105 – Date of Birth 10/5/2005 • 03105 – Date of Birth 4/11/2005

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4. Describe the major operative procedures each animal underwent for research purposes. (e.g., Caesarian sections, craniotomies, etc.)

a. List them by year and protocol number

#26741

9/20/2016 Protocol #15-009 Caesarian Section near term; mother treated with letrozole; male neonate reared to adulthood
8/28/2017 Protocol #15-009 Caesarian Section near term; mother treated with letrozole; female fetus euthanized for analysis of tissues
3/20/2020 Protocol #18-006 Caesarian Section near term; mother untreated (control); female fetus euthanized for analysis of tissues

#26876

4/18/2019 Protocol #18-006 Caesarian Section 1st trimester (day 60); mother treated with estradiol; fetal weight and analysis of placenta and basal plate
1/10/2020 Protocol #18-006 Caesarian Section 1st trimester (day 60); mother untreated fetal weight and analysis of placenta and basal plate
6/17/2021 Protocol #21-003 Caesarian Section near term; mother treated with letrozole and fetus injected once with estradiol and delivered 24h later; female fetus euthanized for analysis of tissues

#27320

2/11/2016 Protocol #15-009 Caesarian Section near term; mother treated with letrozole; female fetus dead in utero (stillbirth);

#07105

12/29/2021 Protocol #21-003 Caesarian Section near term; mother treated with letrozole and fetus injected once with estradiol and delivered 24h later; male fetus euthanized for analysis of tissues

#03105

Protocol #21-003 Currently No major operative surgeries

b. Indicate the dates of IACUC approval and expiration for each protocol

- Protocol #15-009 7/2015 – 6/2018
- Protocol #18-006 6/2018 – 5/2021
- Protocol #21-003 5/2021 – 5/2024

5. What protocol(s) are the animals currently under?

Protocol #21-003

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6. Is it a research, breeding, or holding protocol?	It is a research and breeding protocol. Adult males are only used for breeding.
7. Provide the dates of IACUC approval and expiration of the protocol(s).	Protocol #21-003 5/2021 – 5/2024
8. Why is it necessary to use these animals instead of naïve ones?	<p>As outlined in our previous letter (12/21/2021) these baboons are part of a single developmental study in which we examine the role of estrogen (estradiol) on placental fetal development and offspring function. It is important to prove that the developmental changes in untreated animals and following various treatments are actually occurring in any one animal (fetus or offspring). Thus, it is critical to study the animals at multiple times during gestation and/or after proposed treatments (i.e. multiple surgeries/experimental treatments).</p> <p>Additionally, because each animal can serve as its own control, this reduces variability associated with experimental treatments, which is extremely important from a scientific perspective in demonstrating statistically significant treatment effects.</p> <p>We do and have always enrolled newly purchased (research naïve) baboons into a protocol. However, it is important to recognize that following 3 months quarantine, it takes at least an additional 6 months for newly purchased animals to acclimate to their new environment and achieve a pregnancy. Thus a research naïve baboon may enter the protocol 6 months-1 year (or more) after the protocol is initiated. One experimental treatment typically takes 6 months to complete (pregnancy in baboon = 184 days) but can take up to 14 months in cases where we examine the impact of the hormonal milieu on offspring function in the delivered newborn which is reared by the mother and not weaned until 8-10 months of age. Following completion of an experimental paradigm, an additional 4 months (minimum) is required before this animal is paired with a male and 1-3 more months (1 mating attempt/month) before pregnancy is achieved and a second experimental protocol initiated. Accordingly, there is virtually no way that a research naïve baboon enrolled in a protocol can complete/undergo the treatments required to achieve statistically significant effects. Indeed, as outlined above, (please see response to question 4), no more than 2 experiments were performed in any baboon during a 3-year protocol.</p>
9. Confirm whether the 6 C-sections stated in the request applies to the life of the animal.	Yes; the 6 C-sections stated in the request applies to the life of the animal.
10. What protocol(s) will the	The animals are currently on protocol # 21-003.

animals be
transferred to?

- a. What are the approval and expiration dates of the protocol(s)?
 - Protocol # 21-003 5/2021 – 5/2024
- b. Will they be transferred amongst multiple protocols with the same objective?
 - They will be transferred to one protocol with the same objectives
- c. If so, is the Principal Investigator the same?
 - Yes, the Principal Investigator is the same
- d. What will be the disposition of the animals after the 6th C-section?
 - Euthanasia

Thank you for your timely consideration of this request. Please feel free to contact me directly if additional information is required.

Sincerely,
William J. Wasilenko

Digitally signed by
William Wasilenko
Date: 2022.02.01
11:29:59 -05'00'

William J. Wasilenko, Ph.D.
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WJW/ryoc

cc: Principal Investigator

Rachel Pérez-Baum, DVM, MPH
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February 4, 2022

USDA Animal and Plant Health Inspection Service (APHIS)
Carol Clarke, DVM, DACLAM
4700 River Road, Unit 84
Riverdale, MD 20737-1234
Email: carol.l.clarke@usda.gov

Dear Dr. Clarke:

RE: Eastern Virginia Medical School (EVMS), Norfolk, Virginia
Customer ID: 497
Certificate Number: 52-R-0003
Request for a Multiple Major Survival Surgery (MMSS) Exemption for EVMS Protocol #21-003
Species: Baboon (*Papio anubis*)

In keeping with **AWR §2.31(d)(1)(x)(A)(B)(C)** and on behalf of the EVMS Institutional Animal Care and Use Committee (IACUC), I submit the following information in response to the request for additional information:

EVMS Institutional Animal Care and Use Committee	
1. Complete dates for IACUC approval and expiration for Protocol 21-003.	IACUC #21-003 was approved by the IACUC on May 6, 2021 and will expire on May 5, 2024. IACUC approval is granted for a period of three years; however, continuation of the project beyond the one-year and two-year anniversary dates requires submission and approval of an annual progress report. A new Initial Review Form (IR Form) must be submitted and approved by the IACUC to continue the project beyond the 3-year expiration date. All animal activity ceases on the 3-year expiration date unless or until a new IR Form receives final IACUC approval.
2. Clarify whether the 6 C-sections limit per life of the animal is documented in protocol 21-003 or in a written institutional policy or SOP.	The number of survival surgeries is documented in the protocol. In addition, there is an institutional policy regarding multiple survival surgeries. The protocol includes all the information required in the institutional policy.

3. Conflicting statements about use of naïve baboons.

'We do and have always enrolled newly purchased (research naïve) baboons into a protocol'.....

Females purchased for the project are research naïve when initially enrolled in the project.

'Accordingly, there is virtually no way that a research naïve baboon enrolled in a protocol can complete/undergo the treatments required to achieve statistically significant effects'

There is no way that an individual baboon could complete/undergo the required activities in the 3 years that a single protocol would be approved for. Thus, the reason for the request of moving animals to a new 3-year protocol.

Thank you for your timely consideration of this request. Please feel free to contact me directly if additional information is required.

Sincerely,

(b) (6)

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cc: Principal Investigator

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