Notice of Award

EXPLORATORY/DEVELOPMENT GRANT
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 08/10/2020

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

Grant Number: 1R21TR003191-01
FAIN: R21TR003191

Principal Investigator(s):
Sarah A. Moore

Project Title: SMART IACUC: A path to harmonized veterinary multi-site trial review

Fredson-Cole, Susan
Sponsored Program Officer
B034 Graves Hall
333 W. 10th Ave.
Columbus, OH 432101016

Award e-mailed to: NIHaward@osu.edu

Period Of Performance:
Budget Period: 08/15/2020 – 07/31/2021
Project Period: 08/15/2020 – 07/31/2022

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $240,520 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to OHIO STATE UNIVERSITY in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number R21TR003191. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Shannon Oden
Grants Management Officer
NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

Additional information follows

SECTION I – AWARD DATA – 1R21TR003191-01

Award Calculation (U.S. Dollars)

Federal Direct Costs	$175,000
Federal F&A Costs	$65,520
Approved Budget	$240,520
Total Amount of Federal Funds Obligated (Federal Share)	$240,520
TOTAL FEDERAL AWARD AMOUNT	$240,520
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$240,520

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$240,520	$240,520
2	$242,000	$242,000

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	National Center for Advancing Translational Sciences
CFDA Number:	93.350
EIN:	1316025986A1
Document Number:	RTR003191A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2020

IC	CAN	2020	2021
TR	8014099	$240,520	$242,000

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: 1CCIA21 / **OC**: 41021 / **Released**: eRA Commons User Name 07/31/2020
Award Processed: 08/10/2020 12:04:00 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R21TR003191-01

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1R21TR003191-01

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R21TR003191. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

Additional Costs

SECTION IV – TR Special Terms and Conditions – 1R21TR003191-01

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

SUBJECT FOA
This award is subject to the conditions set forth in PAR-19-100, "Limited Competition: Clinical and Translational Science Award (CTSA) Program: Exploratory Collaborative Innovation Awards (R21 Clinical Trial Optional)," which are hereby incorporated by reference as special terms and conditions of this award. Copies of this Funding Opportunity Announcement can be found at the following link: https://grants.nih.gov/grants/guide/pa-files/PAR-19-100.html

NCATS FUNDING PLAN FOR FY2020
This award reflects the NCATS FY2020 grants funding policy: https://ncats.nih.gov/funding/review/policy.

MODULAR GRANT
This is a Modular Grant Award without direct cost categorical breakdowns issued in accordance with the guidelines published in the NIH Grants Policy Statement, see http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf. Recipients are required to allocate and account for costs related to this award by category within their institutional accounting system in accordance with applicable cost principles.

KEY PERSONNEL
In addition to the PI, the following individuals are named as key personnel (individuals who have effort that NCATS staff is tracking):

Cheryl London

Joan Coates

Written prior approval is required if any of the individuals named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

CONSORTIUM
This award includes funds awarded for consortium activity with **University of Missouri**, **Tufts University**, and **Harvard**. Consortiums are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS, Part II Chapter 15 is available at: http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

PRIOR APPROVAL REQUEST
Any prior approval request (e.g., changes to key personnel as noted on the award, changes in human and animal subjects requiring prior approval, carryover requests) must be submitted in writing by the AOR to NCATSPriorApprovalRequest@mail.nih.gov with a copy to the assigned Grants Management Specialist and Program Official. Please refer to Part II Chapter 8 the NIH Grants Policy Statement for the activities and/or expenditures that require NIH approval at http://grants.nih.gov/grants/policy/nihgps/nihgps.pdf

NON-COMPETING RENEWAL (SNAP)
The NIH requires the use of the Research Performance Progress Report (RPPR) for all Type 5 progress reports. The RPPR and other documents applicable to this SNAP grant are due the 15th of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/15). Please see http://grants.nih.gov/grants/rppr/index.htm for additional information on the RPPR.

ANNUAL FEDERAL FINANCIAL REPORT REQUIREMENT (FOR USE ON NON-SNAP)
An annual Federal Financial Report (FFR, SF 425) is required on this award no later than 90 days after the end of the calendar quarter in which the budget period ends..

The FFR must be submitted electronically through the NIH eRA Commons, available at https://commons.era.nih.gov/commons/. Additional information on electronic submission of FFRs

is available at the Commons eRA Homepage or by contacting the eRA Helpdesk at: commons@od.nih.gov or (866) 504-9552.

COMMUNICATIONS/PRESS RELEASE
If the grantee plans to issue a press release concerning the outcome of NCATS grant-supported research, it should notify the NCATS Office of Communications at 301-435-0888, in advance to allow for coordination.

The NCATS WWW home page is at http://ncats.nih.gov/

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Erin A Davis
Email: davisea@mail.nih.gov **Phone**: 301-827-8026

Program Official: David B. Wilde
Email: wilded@mail.nih.gov **Phone**: (301) 435-0790 **Fax**: 301-480-3661

SPREADSHEET SUMMARY
GRANT NUMBER: 1R21TR003191-01

INSTITUTION: OHIO STATE UNIVERSITY

Budget	Year 1	Year 2
TOTAL FEDERAL DC	$175,000	$200,000
TOTAL FEDERAL F&A	$65,520	$42,000
TOTAL COST	$240,520	$242,000

Facilities and Administrative Costs	Year 1	Year 2
F&A Cost Rate 1	56%	56%
F&A Cost Base 1	$117,000	$75,000
F&A Costs 1	$65,520	$42,000

PI: **Moore, Sarah A.**	Title: SMART IACUC: A path to harmonized veterinary multi-site trial review	
Received: 07/08/2019	FOA: PAR19-100 Clinical Trial:Optional	Council: 01/2020
Competition ID: FORMS-E	FOA Title: Limited Competition: Clinical and Translational Science Award (CTSA) Program: Exploratory Collaborative Innovation Awards (R21 Clinical Trial Optional)	
1 R21 TR003191-01	Dual:	Accession Number: 4328249
IPF: 6218701	Organization: OHIO STATE UNIVERSITY	
Former Number:	Department: Veterinary Clinical Sciences	
IRG/SRG: ZTR1 CI-4 (01)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 125,000 Year 2: 150,000	Animals: N Humans: N Clinical Trial: N Current HS Code: Evaluative Info HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
David Lee-Parritz	Tufts University Cummings School of Veterinary Medicine	Co-Investigator
Helen O'Meara	The Ohio State University	Other Professional-Associate Director, IACUC & IBC
Jeff Henegar	University of Missouri	Other Professional-Dir, Animal Care & Quality Assurance
Valerie Parkison	Tufts University	Other Professional-IACUC/IBC Regulatory Director
Valerie Bergdall	The Ohio State University	Other (Specify)-Other Significant Contributor
Jessica Evans	The Ohio State University	Other (Specify)-Other Significant Contributor
Sarah Moore	The Ohio State University	PD/PI
Joan Coates	University of Missouri	Co-Investigator
Angela McCleary-Wheeler	University of Missouri	Co-Investigator
Barbara Bierer MD	Brigham and Women's Hospital	Co-Investigator
Cheryl London	Tufts University Cummings School of Veterinary Medicine	Co-Investigator

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*
❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

2. DATE SUBMITTED 2019-07-08

Application Identifier

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **Organizational DUNS*:** 832127323

Legal Name*: The Ohio State University
Department:
Division:
Street1*: 1960 Kenny Road
Street2:
City*: Columbus
County: Franklin
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 43210-1016

Person to be contacted on matters involving this application
Prefix: First Name*: Susan Middle Name: Last Name*: Fredson-Cole Suffix:
Position/Title: Sponsored Program Officer
Street1*: B034 Graves Hall
Street2: 333 W. 10th Ave.
City*: Columbus
County: Franklin
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 43210-1016
Phone Number*: 614-292-3097 Fax Number: Email: fredson-cole.1@osu.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1-316025986-A1

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*
● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
SMART IACUC: A path to harmonized veterinary multi-site trial review

12. PROPOSED PROJECT
Start Date* 04/01/2020
Ending Date* 03/31/2022

13. CONGRESSIONAL DISTRICTS OF APPLICANT
OH-003

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Sarah Middle Name: Anne Last Name*: Moore Suffix:
Position/Title: Associate Professor
Organization Name*: The Ohio State University
Department: Veterinary Clinical Sciences
Division: Neurology and Neurosurgery
Street1*: 601 Vernon Tharp St
Street2:
City*: Columbus
County: Franklin
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 43210-1016
Phone Number*: 614-292-3551 Fax Number: Email*: moore.2204@osu.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$529,000.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$529,000.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Susan Middle Name: Last Name*: Fredson-Cole Suffix:
Position/Title*: Sponsored Program Officer
Organization Name*: The Ohio State University
Department: Office of Grants and Contracts
Division: Office of Sponsored Programs
Street1*: B034 Graves Hall
Street2: 333 W. 10th Ave.
City*: Columbus
County: Franklin
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 43210-1016
Phone Number*: 614-292-3097 Fax Number: Email*: fredson-cole.1@osu.edu

Signature of Authorized Representative*
Susan Fredson-Cole

Date Signed*
07/08/2019

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_Letter1040731604.pdf

424 R&R and PHS-398 Specific
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OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	The Ohio State University
Duns Number:	832127323
Street1*:	1960 Kenny Road
Street2:	
City*:	Columbus
County:	Franklin
State*:	OH: Ohio
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	43210-1016
Project/Performance Site Congressional District*:	OH-003

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Missouri
DUNS Number:	153890272
Street1*:	900 E. Campus Dr.
Street2:	Veterinary Health Center
City*:	Columbia
County:	
State*:	MO: Missouri
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	65211-0001
Project/Performance Site Congressional District*:	MO-004

Funding Opportunity Number: PAR-19-100. Received Date: 2019-07-08T16:30:17.000-04:00

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Tufts University Cummings School of Veterinary Medicine
DUNS Number:	039318308
Street1*:	200 Westboro Road
Street2:	
City*:	North Grafton
County:	
State*:	MA: Massachusetts
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	01536-1828
Project/Performance Site Congressional District*:	MA-002

Project/Performance Site Location 3

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	Brigham and Women's Hospital
DUNS Number:	030811269
Street1*:	75 Francis St
Street2:	
City*:	Boston
County:	
State*:	MA: Massachusetts
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	02115-0000
Project/Performance Site Congressional District*:	MA-007

Additional Location(s) File Name:

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ❍ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ❍ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ❍ **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Abstract1040731568.pdf
8. Project Narrative*	Narrative1040730763.pdf
9. Bibliography & References Cited	References1040731569.pdf
10.Facilities & Other Resources	Facilities_and_Other_Resources1040731333.pdf
11.Equipment	Equipment1040731336.pdf

ABSTRACT

While there is no question that experimental animal models are vital to understanding mechanisms of disease and in early-stages of drug development, there is also no shortage of examples where experimental disease models have failed to predict efficacy in human clinical trials. Veterinary clinical trials, using spontaneous animal models of human disease, accelerate successful translation and can assist in rapidly identifying ineffective treatments before progression to human clinical trials. Recent efforts from our group and the broader CTSA One Health Alliance (COHA) community have laid the ground work for integration of veterinary clinical trials into the therapeutic development pipeline by working to standardize trial processes and resources; however, a hurdle to full integration of veterinary clinical trials into the therapeutic development process remains. Presently, institutional animal care and use committees (IACUC) serve, in essence, as veterinary IRBs to review multicenter veterinary clinical trials on a site-by-site basis. Similar to the historical scenario in human medicine, site-specific protocols for approval and monitoring make harmonizing cross-institutional efforts challenging and create inefficiencies and inconsistencies that decrease rigor and reproducibility and increase time to trial completion. To address this hurdle, our proposal aims to build a streamlined platform for single IACUC review and approval of veterinary clinical trials. Building on the NCATS- driven IRB initiative, we will call this platform SMART IACUC. ***We hypothesize that efficiency of veterinary clinical trials can be markedly optimized and enhanced through the design and implementation of a cross-network platform for single review of multi-center veterinary clinical trials called SMART IACUC.*** We will test this hypothesis by first developing a collaborative platform to harmonize veterinary clinical trial review across three partner institutions, educating and training key stakeholders to ensure broad adoption and success of the developed platform across the wider COHA community, and then evaluating and refining the platform using a multi-institutional test case. ***Completion of the proposed work will result in uniform and seamless veterinary clinical trial approval across centers, acceptance of and engagement with the SMART IACUC process across COHA institutions and beyond, and a fully refined platform ready to be deployed as a national resource for translational research.***

PROJECT NARRATIVE

The CTSA One Health Alliance is an organized network of CTSA-affiliated veterinary academic centers with a shared goal of leveraging animals with spontaneous disease, via veterinary clinical trials, to enhance therapeutic development by accelerating successful translation of effective therapies and rapidly identifying ineffective treatments before they progress to human clinical trials. To facilitate efficient integration of veterinary clinical trials into the treatment development pipeline we will build upon ongoing efforts and recent successes with the Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB platform to develop and deploy a SMART institutional animal care and use (IACUC) platform for single, rapid, and rigorous IACUC review and approval of multi-center veterinary clinical trials for use in translational disease research.

FACILITIES AND OTHER RESOURCES

National/CTSA One Health Alliance (COHA)

The institutions included in this application (Ohio State University, Tufts, University of Missouri, and Harvard) are all active Clinical and Translational Science Award (CTSA) program hubs. Drs. Moore, London, Coates, and McCleary-Wheeler are members of CTSA One Health Alliance (COHA). COHA is comprised of veterinary medical schools partnered with medical centers and other colleagues through a National Institutes of Health-sponsored CTSA. COHA's mission is to advance our understanding of diseases shared by humans and animals. The alliance leverages the expertise of veterinarians, physicians, research scientists, and other professionals to find solutions for medical problems and to address the well-being of humans, animals, and the environment. This approach capitalizes on One Health opportunities that accelerate translational research. The current membership encompasses fifteen veterinary medical schools across North America, with new members added frequently based on institutional funding.

One Health is the integrative effort of multiple disciplines working together locally, nationally, and globally to attain optimal health for people, animals, and the shared environment. The COHA group focuses on three key areas in order to accelerate translational research:

1. *Clinical studies subcommittee* (London, Chair; Moore and Coates, members). Research on naturally occurring animal models of human disease. Evaluation of such diseases in a comparative framework can accelerate translational medicine, reduce translational failures and advance human and animal health. Examples include research on cancer, cardiovascular disease, diabetes, shared infectious diseases, arthritis and neurologic disorders. Human-animal interactions that promote health and well-being are also a focus.

2. *Clinician-scientist education subcommittee* (See LOS Trepanier, Chair). An increased number of skilled researchers with diverse perspectives are needed to solve current and future human health problems. Veterinary medical clinician-scientists are underrepresented, yet provide distinctive and essential skills for translational research. Training of future clinician-scientists through technology-enabled and inter-professional graduate/resident curricula will enhance translational research and interdisciplinary collaborations.

3. *Communication and collaboration subcommittee* (See LOS Webb, Chair). Awareness is needed of the capabilities of One Health partners in order to advance translational research. Encouraging formation of collaborative One Health teams will expand problem-solving perspectives and catalyze innovation.

Since its inception in 2014, COHA and its subcommittees have led a number of efforts across the veterinary community to enhance veterinary clinical trial infrastructure and conduct. Resources developed by the group include biobanking resources and standardized procedures, good clinical practice training for veterinarians, and an assortment of other One Health resources. In 2017, in support of increasing the role of veterinary clinical trials in translational research, the COHA Clinical Studies Subcommittee, in conjunction with the OSU CCTS, hosted a two-day workshop focusing on various aspects of trial conduct. Outcomes of this workshop, attended by Drs. Sarah Moore and Joan Coates and organized by Dr. Cheryl London included a standardized informed consent template for use across COHA centers, a GCP training module specific to veterinary medicine, and formalized REDCap training for a representative from all fifteen COHA institutions.

Biobanking resources: Improved translational research opportunities are greatly limited by the availability of high quality biospecimens. While biobanks offer access to those crucial samples, most of the efforts have been in the accumulation and quality of the biospecimens collected and not in expansion of its use. To bridge the gap between these core resources and its users, there is a need to increase awareness of existing biobanks and, at the same time, develop a network of user centric resources. The following veterinary biobanks are engaged in a pilot study to gauge the awareness and interest of biobanks across disciplines: Cornell Veterinary Biobank, Flint Animal Cancer Center Tumor Biorepository at Colorado State University, Texas A&M University Veterinary Small Animal Clinical Sciences Biobank, and the Canine Genetics Biorespository at University of California – Davis

The Ohio State University: Sarah A. Moore, DVM, Principal Investigator and co-investigators O'Meara, and Bergdall

The Ohio State University is the only university in the United States with seven health sciences colleges on one campus, including veterinary medicine, human medicine, dentistry, pharmacy, optometry, nursing, and public health. The OSU College of Veterinary Medicine (CVM) is a 5 minute walk from the OSU Medical Center (MC), and collaboration between researchers in both colleges is common. The physical and intellectual environments at OSU emphasize the "One Health" philosophy, making it an ideal place for important breakthroughs in translational and comparative medicine to occur.

Physical Facilities

Office. Dr. Moore has a dedicated office located in the Veterinary Medical Center (Rm 126). This includes access to fax machines, photocopiers and standard office equipment.

The Veterinary Medical Center (VMC), OSU

As a comprehensive referral center for veterinary practitioners, the hospital is an integral part of the College of Veterinary Medicine at The Ohio State University, and is among the largest facilities of its kind in the world, with more than 35,000 animals examined each year. Faculty, staff and students at the VMC provide specialized care in such areas as orthopedic and soft tissue surgery, oncology, ophthalmology, reproduction, neurology and neurosurgery, urology, gastroenterology, critical care medicine, cardiology, dermatology, radiology, and anesthesiology. Veterinary clinical trials and translational research are an important focus for the VMC and represent an integral part of the mission of the hospital.

The Ohio State University Center for Clinical and Translational Science (CCTS) is a collaboration among the University, The Ohio State University Wexner Medical Center and Nationwide Children's Hospital dedicated to turning the scientific discoveries of today into life-changing disease prevention strategies and the health diagnostics and treatments of tomorrow. Funded by a multi-year Clinical and Translational Science Award (CTSA) from the National Institutes of Health, the CCTS leverages expertise from every college across the University, including scientists and clinicians from the seven Health Science Colleges, the College of Engineering, OSU Wexner Medical Center and Nationwide Children's Hospital, community health and education agencies, business partnerships, and regional institutional network partnerships. The CCTS provides financial, organizational, and educational support to biomedical researchers, as well as opportunities for community members to participate in credible and valuable research. Dr. Moore is the program director for the OSU Comparative and Translational Medicine optional module, which aims to leverage natural animal models of disease, by way of veterinary clinical trials, for use in translational research.

Comparative and Translational Medicine Optional Module (CTM)

Animal models of human disease have been instrumental for generating a comprehensive understanding regarding the biology that drives a multitude of disorders. However, clinical benefits of treatment interventions developed using these models often fail when they are subsequently in humans with the companion diseases. Efforts at improving translational efficiencies have been marginally effective; the likelihood of approval for most treatments that enter human clinical trials remains a dismal average of 10%. While there are multiple reasons for this failure, a major driver is that induced disease models typically lack critical features including diversity in demographics, variability in clinical presentation, and response and resistance to treatment pervasive in human natural disease, all of which influence therapeutic success. Over the past few decades, the concept of "one health" has emerged, based upon the notion that the health of humans is connected to the health of animals and the environment, and that coordinated efforts of multiple disciplines at the local, national and global levels are required to improve the well-being of all. The framework for building a comprehensive one health/one medicine approach already exists at OSU including entities such as the Infectious Disease Institute and the Translational Therapeutics Think Tank. The **CTM** build upon these foundations and leverage natural diseases in veterinary patients to create an integrated platform for collaborative research, therapeutic interrogation, and cross-discipline training and outreach across OSU and its partners. This module supports an interactive research and training enterprise that facilitates multiple efforts to advance translational science. To accomplish these goals, the module has these specific aims: 1) Expand and optimize the use of spontaneous diseases in veterinary patients as models for comparative and translational research by enhancing the existing infrastructure; 2) Develop nodes of comparative medicine in specific disease entities (e.g., cancer, renal disease, infectious disease) that enable rapid advancement in spontaneous model characterization and incorporation into translational efforts; and 3)

Enhance workforce capacity through cross-discipline didactic and hands-on training opportunities, one health driven pilot funding support, and joint outreach/community engagement activities. By incorporating the extensive expertise among the OSU and partner communities, this module has broad impact across the translational landscape. The work proposed in this grant is directly related to long-term goals of this module to enhance veterinary clinical trial infrastructure.

OSU CVM Blue Buffalo Veterinary Clinical Trials Office (CTO) and Veterinary Clinical Research Support Shared Resource (VCRSSR)

The VCRSSR was initially established as the Clinical Trials Office and Biospecimen Repository at the College of Veterinary Medicine in 2007, and is now a developing Shared Resource of the OSU Comprehensive Cancer Center and part of the Comparative Animal Core which is a Shared Resource supported by the Center for Clinical and Translational Studies. The VCRSSR assists in the design, execution, and evaluation of veterinary clinical trials using client-owned animals, with the overriding goal of advancing the diagnosis and treatment of disease in veterinary patients while enhancing the health of humans. Specifically, the office provides guidance with respect to clinical trial design including formulation of a testable hypothesis, determination of patient entry criteria, selection of appropriate toxicity assessments, review of appropriate statistical end points, and development of an accurate budget. The office also confirms compliance with applicable hospital, IRB, and/or IACUC requirements. Case recruitment is enhanced by an established network of regional specialists, veterinarians, and breed clubs to assist with patient enrollment. The office provides education in Good Clinical Practice (GCP), Good Laboratory Practice (GLP), and the requirements of individual organizations sponsoring trials and oversees and verifies correct and complete data entry and compliance with established study guidelines. The Clinical Trial Office supervises an average of 40-50 clinical trials each year, of which 25% are typically multicenter in nature. These studies typically enroll over 600-800 client owned animals into a variety of protocols that involved pharmacokinetic sampling, tissue collection for pharmacodynamic endpoints, and adverse event assessments. The VCRSSR is also responsible for collecting normal tissues/samples and affected tissues/samples from client owned animals presented to the Center. These samples are stored and provided to researchers within the OSU community for interrogation of disease processes and development of new therapies that will impact both animals and humans. Samples collected include fresh frozen and formalin fixed normal tissues (skin, muscle, etc), fresh frozen and formalin fixed diseased tissue (tumors, etc), serum, plasma, PBMCs, and urine. Investigators can arrange for the Repository to collect specific samples prospectively on an as needed basis or to fulfill the requirements of a specific research project. The Repository obtains informed consent from animal owners prior to collection and its activities are covered by an approved IACUC protocol (#2010A0015-R3).

Dr. Cheryl London (joint appointment Tufts and OSU), a Co-I on this proposal, is the **Director of the VCRSSR**. The additional support staff include 1 assistant director (Registered Veterinary Technician – RVT), 1 administrative assistant, 1 biospecimen repository coordinator (DVM), 5 research assistants (RVT or DVM) and a student worker. The VCRSSR consists of 2000 square feet of remodeled office space Square Footage square feet of laboratory space with 12 Dell computers and 2 printers. The VCRSSR at the OSU has access board-certified staff in all specialty areas of veterinary medicine. The Ohio State University College of Veterinary Medicine (OSU CVM) will serve as a the central organizing body for the DM clinical platform trial and the OSU CVM Blue Buffalo Veterinary Clinical Trials Office (CTO) will be responsible for day-to-day management of the clinical trial including management of patient enrollment and data collection across the four trial cites (OSU, University of Missouri, Tufts, North Carolina State University), national marketing of the study, finalizations and quality assurance of all forms. Additional resources associated with the VRSSR include:

- 1 Research Coordinator (RVT)
- 1 Administrative Assistant
- 4 Research Assistants (RVT or DVM)
- 1 Clinical Trials Intern (DVM)
- 1 Student Worker (pre-vet)
- 1000 sq ft of newly remodeled office space
- 7 Dell computers, 2 printers
- Available expert resources; board-certified staff in all specialty areas of veterinary medicine
- Access to 3T & 7T MRI
- PET/CT

- Neuro scintigraphy
- Nuclear Medicine
- Linear accelerator
- DEXA scanner
- Multi-detector computed tomography (MDCT)
- C-arm digital fluoroscopy
- Endoscopy, arthroscopy, laparoscopy, ultrasound, echocardiogram
- 24-hour emergency service with round-the-clock hospital operations

University Laboratory Animal Resources and IACUC.
Ms. Helen O'Meara (co-investigator) is the associate director of OSU's IACUC. The Institutional Animal Care and Use Committee (IACUC) oversees the responsible use of animals in university research and instructional activities, including those associated with the use of client-owned animals (veterinary clinical trials). The IACUC reviews protocols, reviews the animal care and use program, and monitors university animal facilities to ensure compliance with standards and regulatory requirements. Veterinary clinical trials are reviewed by the privately owned animals subcommittee (vet IRB; chaired by Dr. Moore). Informed consent from owners is required to allow animals owned privately to participate in research or teaching and is based on sufficient information (e.g., regarding possible risks and benefits of the activity) and adequate opportunity to consider voluntary participation. Privately owned animals used in research projects are also subject to additional oversight at the College level in addition to IACUC oversight. For College of Veterinary Medicine clinical research, an IACUC protocol will be reviewed by an IACUC subcommittee that has representatives from the CVM to provide input to the IACUC (privately owned animals subcommittee).

Dr. Valerie Bergdall (co-investigator) is the director of OSU's University Laboratory Animal Resources (ULAR) and the Attending Veterinarian for OSU. ULAR at The Ohio State University is responsible for the animal care program which is AAALAC-accredited since 1962 (Accreditation # 028). Over Square Footage square feet of animal housing space in 15 facilities can accommodate rodents, rabbits, swine, ruminants, and dogs as well as other species. Rodent facilities have over 70 dedicated rooms which include barrier housing, sterile housing, phenotyping, and GEM production facilities. Support areas in addition to standard vivaria support are available for all species and include dedicated surgery space Square Footage maging facility (MRI, ultrasound, CT, PET, and IVIS) and necropsy. The program is supported by a staff consisting of a veterinarian ACLAM diplomate, 5 clinical veterinarians, and over 70 fulltime animal care staff. Key animal facilities are listed below:

The Animal Care Program and all animal faculties are AAALAC accredited (#028), registered by the USDA (#31R014) and have Assurances with the Office of Laboratory Animal Welfare, NIH (#A3261-01). The Animal Care Program has 6 veterinarians with 4 of the veterinarians boarded by the American College of Laboratory Animal Medicine (ACLAM) and 65 employees of which 75% are either certified by the American Association of Laboratory Animal Science (AALAS) or registered Animal Health Technicians by the State of Ohio. The ULAR animal care program encompasses all aspects of animal care to include: 1) supervision and monitoring of the humane care and use of animals in research, teaching and testing; 2) veterinary care, emergency veterinary care and veterinary preventive medicine programs; 3) animal husbandry and sanitation; 4) occupational health programs for animal care personnel, faculty and graduate students; 5) environmental health and occupational health safety; 6) radiobiologic safety; 7) procurement and quarantine; 8) quality health assurance; 9) surveillance, diagnosis, treatment and control of disease; 10) zoonoses; 11) assistance to research personnel and investigators in protocol development, procurement, general handling and care; 12) supervision of day-to-day activities. All animals involved in biomedical research at The Ohio State University are observed daily. Health concerns are directed to the attention of the clinical veterinarian and communicated to the principal investigator. Treatment plans are developed as a concerted effort between ULAR and principal investigator staff to determine the most appropriate treatment regime for the animal while considering the research goals and ensuring regulatory compliance. This process is coordinated through laboratory animal health technicians working directly with the laboratory animal residents and clinical veterinarians and relies heavily on the husbandry staff that provides the extensive daily care and observation of all animals in ULAR Vivariums.

Biostatistics Core. Led by David Jarjoura, PhD, this resource helps researchers create and maintain databases, analyze data, develop methodologies and publish results. It assists them in all aspects of experimental design,

data management, statistical analysis, development and application of statistical methods, and manuscript preparation. Consultation is provided by a Departmental MOU and services are provided on an hourly basis for fee.

Technical Support and Services. Technical support is provided for shared equipment, representing an important source of instruction for trainees that supplements that provided by faculty and other staff. Core areas with dedicated staff include Imaging (i.e., flow cytometry, *in vivo* imaging, confocal microscopy), Mouse Phenotyping, Histology and Immunohistochemistry, Biochemistry and Molecular Biology (e.g., real time PCR, surface plasmon resonance), Applied Anatomical and Clinical Pathology. The College employs 3 full time staff members to support the Office of Research and the College-wide Comparative and Veterinary Medicine Graduate Program. As part of the cost share to support the training program the College provides staff time and services to enhance the training environment. Graduate records of the department have been centralized and an inquiry system established to provide information to prospective trainees and graduate students. The Office of Research and Graduate Studies provides administrative support for the research enterprise and graduate education mission of the College. These services include the **CVM Grant Support Office** staffed by a full-time Certified Research Administrator and research scientist who provides administrative support for research conducted in the Department and College. The College of Veterinary Medicine has a **Biomedical Media Department** staffed with a medical illustrator and photographers. This department provides investigators with support for black-and-white and color photography and printing, medical illustration, poster production, computer-designed graphics and imaging, projection slides and video.

Other: OSU Health Science Library: The Prior Health Sciences Library, located adjacent to the Medical Center, contains all major and most minor journals relevant to cancer and other biomedical research. Computerized research sources are available. In addition, access to interlibrary loans is facilitated by trained library staff. Additional library resources are available in the Biological Sciences/Pharmacy Library located on the medical campus. Finally, specialty libraries are maintained by individual departments and may be used by faculty and staff.

Intellectual Environment

Environmental Health & Safety Support. The OSU Office of Environmental Health and Safety (EHS) provides leadership in working with the campus community to provide a safe and healthful environment. They offer training and support for issues dealing with chemical, biological, radiation, hazardous materials as well as workplace safety, personal protection, food and fire safety. EHS works closely with the various safety committees on campus to develop policies and procedures as appropriate for each risk. Written programs are provided to support departmental compliance with the Ohio Public Employment Risk Reduction Program (PERRP) which has adopted federal Occupational Health and Safety Administration (OSHA) regulations and standards to ensure public employees are provided with workplaces free of recognized hazards. Written programs are available for Chemical Exposure Monitoring, Confined Space Entry, Elevated Work, Elevator Safety, Fall Protection, Forklift/Powered Industrial Trucks, Hazard Communication, Heat/Cold Stress, Hot Work, Job Hazard Analyses, Lead Safety, Legionella, Lockout Tagout, Nanoparticles, Noise/Hearing Conservation, Pesticide Handling, Respiratory Protection, Shop Safety, Silica Dust, Trenching/Excavating and Working Alone.

Biosafety. The Research Safety and Biosafety Program focuses on management and regulatory compliance involving the research laboratories at The Ohio State University. Research Safety staff provide consultation services to principal investigators, existing laboratories and staff members throughout the university community. Consultation services encompass a broad range of topics which include laboratory safety, new laboratory set up, assistance with biosafety protocols and procedures, risk assessments, laboratory waste management and comprehensive knowledge of Federal and State Regulations surrounding laboratories. Principal Investigators have primary responsibility for laboratory safety, including containment of biological materials to prevent personnel exposure. Protocols involving the use of recombinant DNA, or are classified as BSL2 or BSL3, must be reviewed and approved by the Institutional Biosafety Committee. EHS monitors laboratories to be sure that biological materials are handled and stored safely. Environmental Health and Safety (EHS) conducts routine university wide laboratory safety inspections with the intent to reduce risk, determine compliance with Federal and State regulations and to promote a culture of safety. Inspections encompass chemical, biological and hazard communication topics and are conducted in the presence of a laboratory employee familiar with the operations.

Inspections are announced and often times scheduled with the process typically taking between 20 to 40 minutes. Each year laboratories are encouraged to obtain a copy of the revised laboratory safety checklist and to perform periodic self-inspections. The self-inspection process allows groups the opportunity to raise awareness to the risks while promoting a safety culture within the laboratory.

Brigham and Women's Hospital and Harvard: Barbara Bierer, MD, Co-investigator

Multi-Regional Clinical Trials (MRCT) Center of Brigham and Women's Hospital and Harvard: The MRCT Center (Dr. Bierer, Faculty Director) is a research and policy center associated with two of the world's most respected names in healthcare and academia: Brigham and Women's Hospital and Harvard University. A specific focus area for the MRCT Center is tackling critical issues in the ethics, design, conduct and oversight of trials to maximize safety and rigor, and to develop practical and pragmatic guidance, resources and tools. Our multidisciplinary teams collaborate to identify challenges and deliver ethical, actionable, and practical solutions for the global clinical trial enterprise, with a focus on emerging economies. Our efforts have resulted in the implementation of improved clinical research practices, greater transparency, and improved safety for research participants. We function as an independent convening group to bring together collaborative multidisciplinary teams to identify expert stakeholders from industry, academia, advocacy groups, nonprofit organizations, and regulatory agencies to address critical issues in the conduct and oversight of clinical trials. The vision of the MRCT Center is to improve the integrity, safety, and rigor of global clinical trials by identifying regulatory, oversight, and ethics issues and facilitate solutions in clinical trials around the world; resolve regulatory and ethical issues in order to improve the clinical trial enterprise; foster respect for clinical trial participants by working to improve the ethics, safety and transparency of clinical trials; and promote regulatory convergence within multiple regions to accelerate innovation and improve health care around the world.

The "MRCT Project" was initiated in 2009 by Pfizer Inc. at a summit meeting held at Harvard University with a group of diverse stakeholders. The output of the summit meeting culminated in a report of recommendations that led to the establishment of the Multi-Regional Clinical Trials (MRCT) Center. The report also served as the blueprint for the Center's first three initiatives. The mission of the MRCT Center was defined as to focus on the design, conduct and oversight of multi-regional clinical trials with an emphasis on those issues involving the emerging economies. Starting in 2010, additional industry, non-profit and academic stakeholders joined the MRCT Center as members of the Executive and Steering Committee, forming a diverse stakeholder community of like-minded organizations to address the common challenges associated with globalization of clinical trials. Numerous projects and workstreams were launched including Post-Trial Access to Medicines, Return of Results, and Core Competencies in Clinical Research Professionals. In 2013, the MRCT Center launched a workstream to address data sharing and transparency that, among other issues, envisioned a platform to enable access to clinical trial data with the capacity to combine data sets. In 2017, the MRCT Center launched Vivli, a Center for Global Data Sharing, that was incorporated as a separate 501(c)(3) entity.

The MRCT Center is located on the Harvard University campus and at the Brigham and Women's Hospital and administratively associated with the Division of Global Health Equity at the Brigham and Women's Hospital. We are supported by a vibrant community of stakeholders and focus our unique expertise into four Focus Areas: Transparency; Ethics, Conduct, and Oversight; Global Regulatory Engagement; and Capacity Building. Please see our Projects page for a list of our current projects and workstreams. Our in-country engagements have included China, India, and Mexico. The MRCT Center has trained representatives from 25 countries. Our collaborative community includes approximately 2000 people from 30 countries. Since the mission of the MRCT Center is to impact the emerging and developing world, our resources and tools are, most often, freely and openly available. Selected versions of tools and resources are available to sponsors only for six months prior to public release on our website for download.

National SMART IRB Reliance Initiative: SMART IRB (the Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform) is designed to harmonize and streamline the IRB review process for multisite studies, while ensuring a high level of protection for research participants. Dr. Bierer is the Director of Regulatory Policy for SMART IRB. SMART IRB is not an IRB; rather, it's a platform that offers a master IRB reliance agreement (the SMART IRB Agreement) and a web-based system (SMART IRB's Online Reliance System) that provides a central process for participating institutions and their investigators to request, track, and document study-specific reliance arrangements. Investigators and their study teams, together with

institutional and HRPP/IRB offices, use the SMART IRB platform to initiate single IRB review of a study. SMART IRB also provides a gateway to essential education as well as flexible tools and resources designed to support the adoption and implementation of single IRB review for a range of studies. Launched in 2016, SMART IRB is currently funded by the NIH Clinical and Translational Science Awards (CTSA) Program, grant number UL1TR002541-01S1. The platform serves as a roadmap for institutions to implement The National Institutes of Health (NIH) Policy on the Use of a Single Institutional Review Board for Multisite Research effective January 2018, though SMART IRB may be used for any study that is eligible for IRB reliance, regardless of funding source or status.

An important goal of SMART IRB is to harmonize the clinical trial landscape by taking a strategic, efficient and cooperative approach to single IRB review. As institutions apply diverse approaches to implementing single IRB review, new burdens and challenges emerge for investigators, collaborating institutions, and IRBs. One of the goals of SMART IRB is to harmonize these diverse approaches by promoting not only the alignment of policies and processes, but also the adoption of common forms and identification of common practices and workflows. To date, a variety of guidance documents have been developed and approved by the leaders of SMART IRB and topic experts who comprise the harmonization steering committee and its working groups following consideration of public review and comment. Examples of these include recommendations for reportable events in investigator-initiated multisite studies, documenting institution-specific information about IRBs, and institutional versus IRB responsibilities guidances. Resoures developed by SMART IRB are available to investigators via the website smartirb.org.

A series of web-based systems to support the SMART IRB Agreement are available:

The **Joinder** tool facilitates the process for an institution to request to join the SMART IRB platform, as well as the administrative process to confirm eligibility and establish points of contact, and institution profiles.

The SMART IRB **Online Reliance System** facilitates and documents the decision-making process on a study-by-study basis. Through this system, an investigator (or designee) requests IRB reliance, and the institutions involved reach a reliance determination. The system tracks who needs to take action, automatically notifies the next person when a handoff occurs, and provides a central location for the reliance determination. This platform:

- Simplifies the selection of a single IRB for multisite studies
- Manages communication between institutions and investigators
- Tracks the status of requests
- Clearly indicates what needs to be done next
- Documents reliance arrangements for each study
- Reminder options help keep the process moving
- Sites can be added to a reliance arrangement by amendment
- Provides On-demand summary reports for institutions

University of Missouri: Co-investigators Coates, McCleary-Wheeler, and Henegar

The University of Missouri at Columbia is one of a small number of universities across the country that houses a School of Medicine, a College of Veterinary Medicine, a School of Engineering and other schools involving the health professions on the same campus. This proximity allows for easy access to experts in areas of human and animal biomedical research and fosters cross-disciplinary interactions and collaborations. Dr. Coates' home department, Veterinary Medicine and Surgery, takes advantage of this, with many of the veterinarian clinician researchers participating in the One Health, One Medicine strategic initiative of Mizzou Advantage. Researchers collaborate across departmental and disciplinary boundaries to share information and expertise to foster new approaches to human and animal medicine.

Drs. Coates and McCleary-Wheeler, both clinicians in the Veterinary Teaching Hospital, have established a network of interdisciplinary collaborators on the MU campus through the Comparative Neurology and Oncology Programs. The relevant facilities at the University of Missouri consist of the Veterinary Health Center, the

Veterinary Medical Diagnostic Laboratory, the Office of Animal Resources, and a number of shared core service facilities.

Department of Veterinary Medicine and Surgery (VMS). The VMS Department provides significant administrative support for faculty through administrative assistants and pre- and post-award grant support. The VMS department also oversees the internship and residency programs and faculty mentorship programs. A majority of Dr. Coates' salary support is through the Department of VMS and the Veterinary Health Center.

College of Veterinary Medicine Office of Research and Graduate Studies. The Office for the Associate Dean of Research facilitates transmission of research opportunities that may benefit faculty and graduate students in the College of Veterinary Medicine. The office also facilitates processing of grants within the three departments of the College. Specifically, the Department of Veterinary Medicine and Surgery has a person dedicated to management of grants pre-and post-award.

Office of Sponsored Programs Administration. The MU Office of Sponsored Program Administration has a post-award staff of 16 individuals who oversee grant and contract expenditures of over $210 million annually. A full set of standard operating procedures and internal controls are in place to monitor spending and compliance for grants and contracts. A full accounting and procedure manual detailing internal fiscal controls is available at http://www.umsystem.edu/ums/departments/fa/controller/accountingservices/manual/ The departmental and divisional management teams work directly with an assigned accountant in the MU Office of Sponsored Programs, who negotiates billing, monitors compliance and auditing and provides fiscal accountability to granting agencies.

Mizzou Advantage. The Mizzou Advantage is the result of a three-year strategic planning process. Its goal is to strengthen relationships among faculty, centers and departments, and to build networks, internal and external, of very high-achieving individuals and organizations that will be even more competitive than now for very large grants and contracts, for attracting the best faculty and students to MU, and for gaining recognition for our faculty (e.g., election to the National Academy of Sciences) and students (e.g., being employed in the best university and corporate positions). Efforts in this involve networking activities to build relationships, to seed new and productive collaborations, and to deepen MU's presence in each of the four initiatives 1) One Health, One Medicine: The Convergence of Human and Animal Medicine, 2) Food for the Future, 3) Media for the Future, and 4) Sustainable Energy.

Office and Computer

The office for Drs. Coates and McCleary-Wheeler have approximately 100 sq ft, offices located in the Veterinary Health Center (VHC), which allows for easy access to all of the clinical facilities at the hospital. Departmental administrative and information technology support are available from staff housed in two nearby administrative suites in the VHC and the Veterinary Medicine Building. Both have Dell personal desktop and laptop computers and HP printers, with the necessary software for coordinating the efforts of collaborators, analyzing data, and preparing publications. We have access to a large library of software as well as to a large collection of software licensed by the University from many vendors. All computers are net-worked through the MU system to allow for data sharing and communication and are connected to the world-wide-web.

Veterinary Health Center – Small Animal Hospital (VHC-SAH)

The College of Veterinary Medicine is a fully accredited College of Veterinary Medicine by the American Veterinary Medical Association. The VHC is the premier veterinary referral center in the state of Missouri. The VHC has Square Footage square feet dedicated to the small animal hospital, including separate areas for oncology, cardiology, ophthalmology, dermatology, dentistry, physical rehabilitation, nutrition, neurology and neurosurgery, orthopedic surgery, soft tissue surgery, internal medicine, community practice, theriogenology, anesthesiology, radiology 24-h emergency and intensive care unit, full service clinical pathology laboratory, in-house pharmacy, radiation therapy and imaging. The VHC, located across a small parking lot from the Veterinary Medicine Building in Clydesdale Hall (900 East Campus Drive). The MU VHC offers the latest in neurodiagnostic tests that include advanced imaging, electrodiagnostic testing (Cadwell Sierra Summit), cerebrospinal fluid analysis, and DNA testing. Imaging modalities available in house include computed tomography (CT) (Helical-64 slice, Toshiba), 3.0 Tesla magnetic resonance scanner (Toshiba), fluoroscopy (OEC 990 Elite, GE) and CT/Positron Emission Tomography scanner (Celesteion PET/CT scanner, Toshiba). The VHC-SAH also has a newly

established Motion Analysis Laboratory for kinetic and kinematic evaluation of gait. A state-of-the-art intensive care unit is available for the dogs if intensive monitoring is necessary. The VHC has been visited and approved by personnel from the U.S. EPA, USDA and the U.S. Army Center for Health and Preventative Medicine Health Effects Research Program. The MU VHC has dedicated and ALAAC, AVMA and AAHA approved animal facilities and a completely digital hospital information and digital on-line radiology systems. The Veterinary Health Center provides a supportive environment for clinical trial research and has experience in performing veterinary clinical trials.

University of Missouri Partnerships Relevant to the Proposed Project
Washington University, Institute of Clinical and Translational Science (ICTS).
The University of Missouri is a partner with the Washington University ICTS (http://icts.wustl.edu/), funded through a multimillion dollar grant from the NIH Clinical Translational Science program. Washington University ICTS offers competitive funding opportunities to researchers at the University of Missouri and other Washington University ICTS partner institutions. Various funding opportunities are available, including 1-year grants for pilot projects and 2-year KL2 career development grants, modeled after the NIH career development program. Researchers from partner institutions are also eligible to apply for other competitive funding programs administered through the Washington University ICTS. Members of ICTS also have access to resources located at Washington University, including an array of core facilities and the availability of experts on study design, data interpretation, and the translation of basic research to clinical application.

University of Missouri Core and Research Support Facilities
The University Office of Research operates numerous state-of-the-art Core Facilities http://research.missouri.edu/about/cores. In addition, we will employ the services of the Office of Animal Resources for oversite of the clinical trial research on companion animals at the University of Missouri.

Office of Animal Resources (http://oar.missouri.edu/)**.** Mr. Jeff Henegar (co-investigator) is the Director of Animal Care Quality Assurance in the Office of Animal Resources at MU. The Office of Animal Resources approves all procedures performed on companion owned dogs and evaluates informed consent documents associated with these studies. This service department is directed by a Diplomate of the American College of Laboratory Animal Medicine and staffed by additional laboratory animal veterinarians and AALAS-certified technicians and technologists.

The Institutional Animal Care and Use Committee (ACUC) ensures that investigators comply with best-practice standards review all animal procedures. The University of Missouri uses the designated member review method for animal protocol review. The ACUC Chairperson is responsible for reviewing and granting final approval of all animal use protocols (unless he/she assigns a designated reviewer or the protocol application is called for convened full committee review). The University of Missouri's protocol approval process, as described in its Assurance Statement that has been approved by the Office of Laboratory Animal Welfare, is presented below.

For all new protocol applications (including those that have the potential for causing pain and distress to animals) the PI completes and signs the Animal Care and Use Protocol application form and submits it to the ACUC coordinator. The ACUC coordinator reviews the application for completeness. The ACUC coordinator and the Animal Care Quality Assurance Office Director then determine together if a clinical veterinarian needs to review the protocol. Veterinary review is required if the study may involve more than minor and transient pain and distress.

If no veterinary review is required, the protocol is assigned to a voting member of the ACUC, who performs the pre-evaluation. If veterinary review is required, the protocol is assigned to a clinical veterinarian in the Office of Animal Resources. The veterinarian will review the protocol for the adequacy of surgical and nonsurgical procedures, anesthesia, and method(s) of euthanasia. The veterinarian also will review for the potential for pain or physical stress, and for procedures with potential to cause pain in which analgesics, anesthetics, or tranquilizers will not be used to control pain. Changes and/or corrections in these areas will be agreed upon by both the applicant and the veterinarian, and noted on the application.

Following veterinary review, the ACUC coordinator will assign the protocol application to a member of the ACUC, who performs a pre-evaluation. The ACUC member who performs the pre-evaluation (e.g., the pre-evaluator)

is responsible for reviewing the entire application to ensure that it complies with regulations of the Animal Welfare Act and Public Health Service Policy. Changes and/or corrections to the protocol application will be agreed upon by both the pre-evaluator and the applicant, and noted on the application. The pre-evaluator will then make one of four recommendations to the ACUC: 1) approval, 2) require modifications, 3) defer for clarification, or 4) disapproval. The pre-evaluator's recommendation of "requires modification," "defer for clarification," or "disapproval" sends the protocol to convened ACUC review.

Following pre-evaluation, the ACUC coordinator sends to each ACUC member a copy of the project title, a justification of the proposed experimentation, the number and specification of animals to be used, and a description of the role of animals, which provides an opportunity to request, by a prescribed date, for the convened ACUC review of any protocol.

Protocols recommended for approval by the pre-evaluator, and for which there is no request for convened ACUC review before the prescribed date, are forwarded to the ACUC Chairperson to review and approve under the designated reviewer method, or to appoint a designated reviewer. Any ACUC member may request convened ACUC review of any protocol at any time during the review process or after it has been approved.

For protocols under convened ACUC review, the convened ACUC action, by majority vote, may be: 1) approval, 2) disapproval, 3) requires modifications, or 4) defer for clarification. The ACUC coordinator will communicate the results to the PI. ACUC decisions of "disapproval," "require modifications," and "defer for clarification" include the reasoning and/or requirements of the ACUC for changes necessary to secure approval.

Approval of minor amendments to approved protocols can be obtained by submission of an Animal Care and Use Protocol Amendment to the ACUC Chairperson. The ACUC Chairperson may approve a minor amendment if it does not significantly impact issues of animal pain and distress.

The ACUC conducts continuing review of each previously approved ongoing activity covered by the Policy at appropriate intervals as determined by the ACUC. This includes a complete review at least once every three years in accordance with the Public Health and Safety Policy.

Environmental Health & Safety Support. The MU Office of Environmental Health and Safety (EHS) provides leadership in working with the campus community to provide a safe and healthful environment. They offer training and support for issues dealing with chemical, biological, radiation, hazardous materials as well as workplace safety, personal protection, food and fire safety. EHS works closely with the various safety committees on campus to develop policies and procedures as appropriate for each risk.

Biosafety. Biosafety is a complete program of recognition, evaluation, and control to minimize the health risk from potential exposure to biohazardous materials that are used in research and teaching activities at MU. Principal Investigators have primary responsibility for laboratory safety, including containment of biological materials to prevent personnel exposure. Protocols involving the use of recombinant DNA, or are classified as BSL2 or BSL3, must be reviewed and approved by the Institutional Biosafety Committee. EHS monitors laboratories to be sure that biological materials are handled and stored safely.

University of Missouri-Columbia Research Support Computing Group in the Division of Information Technology. The Research Support Computing (RSC) group within the Division of Information Technology (IT) provides computer-related assistance to the research community at MU. This support involves soliciting input from researchers throughout the campus to assess needs for specialized, high-performance computing and networking resources, ensuring that the campus computing and networking infrastructure is positioned to support these needs and to provide education, training and consulting to take maximum advantage of the available resources.

As part of its ongoing efforts, the RSC has built the foundations for supporting MU researchers by establishing a high-speed networking connection to national Internet network. The RSC also provides high-speed research network infrastructure on campus to support high-performance, network-based applications as well as substantially increasing the computational and data storage capacities available to researchers for

computationally and/or data intensive activities. These facilities also provide opportunities for researchers to partner with others at peer institutions as part of the Internet activities.

Tufts University: Co-investigators London, Lee-Parritz and Parker

CUMMINGS VETERINARY REFERRAL CENTER

The recently renovated and enlarged Henry and Lois Foster Hospital for Small Animals provides 24-hour care for pets 365 days of the year. Since 1979, the hospital has offered consultation, referral, and emergency veterinary services for the care of dogs, cats and exotic pets. With faculty specialists in every field of animal medicine and the region's most powerful diagnostic imaging capabilities, the hospital staff can diagnose and treat even the most difficult and complex conditions. Veterinary specialties include MRI, ultrasound, CT and a state of the art interventional radiology unit, facilitating surgical procedures such as the placement of stents and pacemakers. There hospital also has advanced critical care, anesthesia, pain management and advanced radiation oncology for animal cancer patients. The teaching hospital is on the forefront of cutting-edge medicine,

As a major tertiary referral center for the New England region, the annual number of patient visits exceeds 30,000 (FY2016, 33,806) and the affiliated Tufts VETS satellite specialty practice (tuftsvets.org) had approximately 20,000 patient visits, making this the largest single academic referral network in the country. The hospital employs over 50 veterinarians that are board-certified in numerous specialties. The ***Emergency Service and Intensive Care Unit*** is home to the largest veterinary critical care training program in the country. The Emergency and Intensive Care services provide care for over 17,000 cases per year, and serve as one of the busiest academic hospitals in the nation. The service has the ability and experience to provide all levels of intensive care including intermittent positive pressure ventilation, transfusion, and support of the multiple-organ failure patient. Diagnostically, the EIC has 24-hour/day CT scanning capabilities, as well as round-the clock laboratory support. A critical care resident or faculty member is attending 24 hours a day. Nursing care is provided by specially trained and certified nurses (CVT-VTS)."

Office and Computer

The offices of Drs. London and Lee-Parritz, and Ms. Parkison are located in comfortable faculty office buildings maintained by the facilities and by the departmental IT service. They contain Dell personal desktop and laptop computers and HP printers with the necessary software for coordinating the efforts of collaborators, analyzing data, and preparing publications. We have on-line and physical access to a large library of books, journals, software as well as to a large collection of software licensed by the University from many vendors. All computers are net-worked through the Tufts University system to allow for data sharing and communication and are connected to the world-wide-web.

University Laboratory Animal Resources: Dr. David Lee-Parritz (co-investigator) is the Director of Laboratory Animal Medicine (LAM) at Tufts. Ms. Valerie Parkison (co-investigator) is the IACUC/IBC regulatory director. The LAM program faculty include 3 full-time faculty from Cummings School of Veterinary Medicine at Tufts University (Drs. Karas, Lee-Parritz, Warner). Additionally, the program faculty includes veterinary experts from Charles River Laboratories, University of Massachusetts Medical School, Genzyme, Tufts Medical Center, Massachusetts Institute of Technology, Wyeth Laboratories, and Massachusetts General Hospital Animal Facilities. The Laboratory Animal Medicine Service provides facilities, services and information to in support of high quality biomedical research and teaching with animals at Cummings School of Veterinary Medicine at Tufts University. Members of the service ensure that animal care and use procedures comply with federal, state and local regulations. The management and operation of the animal care activities of all sites assure implementation of a high quality animal care and use program. Internal and external investigators carry out a wide variety of research projects with a wide range of animal species, including livestock. A high level of client service, strong veterinary expertise, effective technical service delivery, quality animal housing, compliance with federal and state regulations and maintenance of AAALAC accreditation characterize this program.

RESEARCH ENVIRONMENT

The ***Tufts Clinical and Translational Science Institute*** was established in 2008 with a Clinical and Translational Science Award (CTSA) from the National Institutes of Health (NIH) and support from Tufts Medical

Center and Tufts University. Tufts CTSI spans all the schools of Tufts University, its affiliated hospitals across Massachusetts and Maine, participating universities, community organizations, and non-profit and for-profit organizations. Educational resources include the MS/PhD Clinical and Translational Science Program at the Tufts University Sackler School of Graduate Biomedical Sciences and CTS certificate program, as well as ongoing research training seminars and workshops. Tufts CTSI's integrated home administrative offices are located on the 8th floor at 35 Kneeland Street in Boston, MA. Our offices occupy an 8424 usable square foot area that is centrally located on the Tufts Health Sciences Campus and physically connected to the Tufts Medical Center and the Tufts University School of Medicine, and adjacent to the schools of Dental Medicine and Nutrition. The space includes 24 private offices for faculty and staff and nine cubicles available for trainees, each with desktop computers. Within this space are three multi-purpose conference rooms that are equipped with state-of-the-art audiovisual tools, including production and training equipment such as video conferencing and large LED panels. A large common room equipped is designed to promote collaborative activities and to develop new informatics and interactive educational applications. Our offices are well equipped with ample necessary office equipment. Visitors and staff have the option to use the wireless network capabilities of the area. Located nearby on the 6th floor of the Farnsworth building in Tufts Medical Center is the Clinical and Translational Research Center (CTRC), a core institutional resource dedicated to promoting patient-oriented research. The CTRC has 6,484 square feet of clinical research space available for investigators to conduct clinical studies. It is equipped with a 10-bed inpatient unit equipped with Wi-Fi, 3-chair phlebotomy/infusion clinic, 12 outpatient exam rooms, metabolic research kitchen, administrative staff offices, a sample preparation laboratory, and centrally located computer work area. The CTRC also has storage space for study equipment, conference rooms, EKG, scales, monitoring equipment, infusion devices, emergency cart, laboratory transport system, and a locked medication room. Faculty and trainees of all Tufts CTSI affiliated partners can utilize CTRC services for clinical studies. In addition, the CTRC Core Laboratory occupies 2,228 square feet on the 7th floor of the Ziskind building and is available for analysis of samples collected in clinical research protocols, scholar and trainee research projects and Tufts CTSI pilot awards.

The Veterinary Clinical Trials Office (CTO): This office is staffed by 3 certified veterinary technicians and will be moving into a newly remodeled space in May of 2017. Consisting of 1000 sg ft of office space, a Square Footage laboratory dedicated to processing trial specimens, and an adjacent dedicated conference room with conferencing capabilities. The CTO laboratory has a -80C freezer, -20C freezer, a 4C refrigerator, a refrigerated centrifuge for spinning biospecimens (i.e., PBMCs, etc), a desktop centrifuge for blood samples, and a large vapor phase storage liquid nitrogen tank, as well as the necessary tools for processing samples. The associated Clinical Research Laboratory provides services including qPCR, specialized coagulation testing, platelet function testing, and ELISA based testing.

Biosafety Laboratory: The Tufts New England Regional Biosafety Laboratory (RBL) is a Square Footage square foot resource available to researchers in industry, academia, government and not-for-profit, dedicated to the study of existing and emerging infectious diseases, toxin-mediated diseases and medical countermeasures important to biodefense. The Tufts New England Regional Biosafety Laboratory is a regional resource that will allow researchers to improve human health through better detection, prevention and treatment of infectious diseases.

Global Health Program: Cummings School is committed to advancing One Health initiatives that enhance the health and well-being of animals, humans and the environment. The leadership in both clinical and research settings reaches across disciplines, into the classroom, and out in the world. Our faculty engages in innovative One Health research in the areas of infectious disease, comparative oncology, international medicine, wildlife, conservation medicine and human-animal interactions. This work creates a campus without boundaries, offers unique learning experiences, and ultimately helps us educate a new breed of One Health graduates prepared to make a positive impact in the World.

AFFILATED HOSPITALS

Tufts Medical Center serves as the principal teaching hospital for Tufts University School of Medicine and provides comprehensive inpatient and outpatient care in every specialty. At the middle of the Tufts Health Sciences Campus, adjoining a large Asian community and Boston's other diverse neighborhoods; Tufts Medical Center has 415 licensed beds and over 500 attending physicians. It operates a full service Emergency Department, Pediatric Emergency Department and Level I Pediatric Trauma unit with approximately 35,000 emergency/trauma visits per year, and it is equipped with a rooftop helipad. Numerous clinic practice sites are

available, including hospital-based offices, neighborhood health centers, community physician practices, and HMOs. Tufts Medical Center and Floating Hospital for Children ranked among the top 7% of award recipients of NIH research funding in FY 12, with a nearly 20% increase in NIH funding from the previous fiscal year. As the physical home to the Tufts CTSI, Tufts Medical Center has excellent computer capacity through its system network, which connects all hospital departments and divisions via desktop personal computers as well as Internet access. Tufts Medical Center staff members have full access to the Tufts University library and online databases via the network. Office and conference space is provided by Tufts Medical Center. Additionally, a copy center and educational media services are available to all faculty and staff throughout Tufts Medical Center, as are support services such as the Tufts Institutional Review Board, research administration and finance, human resources, purchasing, telecommunications, building maintenance, and other systems support.

Tufts Medical Center is home to several active and productive research institutes, which are supported by a broad spectrum of service core facilities. ***The Tufts Center for Neuroscience Research*** (CNR) was established in 2003 with funding from the National Institute for Neurological Disorders and Stroke (NINDS) and generous support from Tufts University School of Medicine (TUSM) and Tufts Medical Center. The primary goals of the CNR are to support neuroscience research efforts and to promote collaborative interactions among neuroscientists at Tufts University and its affiliated hospitals. The CNR is located within the TUSM Department of Neuroscience; it provides core research services to Tufts neuroscientists and other investigators. CNR-supported core facilities offer services for biological imaging, computational genomics, and animal behavior. The establishment of the CNR and the operation of the core facilities are greatly aided by support from Tufts University, TUSM, Tufts Medical Center and a continuing center core grant from the NINDS. As an indication of center productivity and its usefulness in research at Tufts, it is important that investigators acknowledge the use of CNR core facilities and assistance in their research publications. ***The Molecular Oncology Research Institute*** is home to 17 faculty members focused on all aspects of cancer research. MORI researchers are actively investigating mechanisms of breast, brain, bone and blood cancers. The ***Molecular Cardiology Research Institute*** has 17 faculty members work with over 80 scientists and physician scientists to address molecular mechanisms of cardiovascular disease and develop new therapeutic approaches to these disorders. The newly established ***Mother Infant Research Institute*** at Tufts Medical Center focuses on the lifelong consequences of the intimate and unique biological relationship between mother and baby during pregnancy. MIRI is the only research institute in the United States that combines pediatrics and obstetrics to investigate the impact of events that occur during pregnancy on trans-generational health. MIRI's current research centers on preterm birth and its complications, the adverse effects of maternal obesity, and fetal and neonatal personalized medicine. MIRI's guiding principle is that clinical and translational multi-disciplinary research directed towards ensuring healthy pregnancies, full- term deliveries, and normal birth weights will positively affect both health and health care costs for millions of people at all stages of the life cycle.

The ***Biostatistics, Epidemiology and Research Design Center (BERD)*** is comprised of a free pre-award research design and preliminary analysis center, and the Biostatistics Research Center, the fee-for-service post-award data management and analysis and methods research center. Both centers are staffed by epidemiologists and statisticians, many of whom also serve as faculty within our CTS Graduate Program in the Sackler School of Biomedical Sciences. The combined centers promote innovation and excellence across the spectrum of patient-oriented research through development of new statistical and study design methods, provision of training and education, collaborative support in applying standard and cutting-edge design and analytic techniques.

MAJOR EQUIPMENT

The Ohio State University, Sarah A. Moore, Principal Investigator, O'Meara, Bergdall, co-investigators

Research Electronic Data Capture (REDCap),
REDCap is a secure, web-based application designed to support data capture for research studies by building and managing online surveys and databases. REDCap's streamlined process helps to rapidly develop projects, using 1) the online method from a web browser using the Online Designer; and/or 2) the offline method by constructing a 'data dictionary' template file in Microsoft Excel, which can be later uploaded into REDCap. Both surveys and databases (or a mixture of the two) can be built using these methods. REDCap also provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R). REDCap also includes a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields. The **REDCap Consortium** is comprised of 312 active institutional partners from CTSA, RCMI and other institutions across the globe. Specific to OSU's veterinary clinical trials office and this project, Ms. Ashley Smith (key personnel on this project) has received extensive REDCap training and is experience in the build, maintenance, and administration of REDCap data collection forms. Additionally, the OSU CCTS employs a bioinformatics specialist focusing on REDCap. REDCap accounts, training and consultation are offered to OSU investigators, faculty, and staff at no cost. Additional technical support for new builds with in REDCap is available from CCTS for this project for an hourly fee. Dr. Sarah Moore has also undergone extensive REDCap training and is familiar with the use of this platform in the context of electronic study record reporting. She has also served as the PI on the builds for two longitudinal veterinary patient registries using the REDCap platform.

Veterinary Medical Center – Hospital for Companion Animals
Equipment for clinical evaluation of companion dogs for an assortment of veterinary diseases with translational significance. This includes a dedicated surgical suite for sterile procedures involving OSU veterinary patients and all required surgical instruments. General anesthesia in client-owned dogs is induced and monitored at all times by a veterinary technician-anesthetist under direct supervision of one of our four board-certified veterinary anesthesiologists. Available Imaging equipment includes digital radiography and fluoroscopy (GE DRS 3.2) for routine radiography and contrast studies, ultrasonography (Acuson Sequoia 512), computed tomography (GE LightSpeed Ultra 128 slice/sec), and magnetic resonance imaging (Achieva, Phillips 3.0T).

Clinical Diagnostic Laboratories
Our clinical diagnostic laboratories provide reliable, accessible, cost-effective, efficient and innovative laboratory diagnostic testing across multiple lab sections including Applied (Anatomic) Pathology, Clinical Pathology, Microbiology and Parasitology. The labs also work closely with our on-site Animal Blood Bank. The collective professional expertise of the Clinical Diagnostic Laboratories supports the teaching, service, research and outreach missions of the Ohio State University College of Veterinary Medicine including all Ohio State University Veterinary Hospitals in the Veterinary Medical System, as well as veterinary practitioners and researchers. The Applied Pathology Service has an approximately Square Footage square foot necropsy laboratory equipped with tables, necropsy implements, a band saw and all equipment needed to perform the postmortem examination.

The Ohio State University Veterinary Clinical Research Support Shared Resource (VCRSSR):
Shared equipment includes 2 Thermo Scientific Forma-80 Celsius ultra-low freezers, Thermo Scientific Revco flammable materials refrigerator, Fisher Scientific Isotemp -20 Celsius freezer, Frigidaire refrigerator, Beckman-Coulter GS-6KR centrifuge, Eppendorf 5414D ultra-centrifuge, Taylor-Wharton Labs-40K liquid nitrogen freezer, Nuaire laminar flow hood, available expert resources; access to 3T MRI on site, PET/CT, neuro scintigraphy, nuclear medicine, linear accelerator, DEXA scanner, 128 slice Multi-detector computed tomography (MDCT), C-arm digital fluoroscopy, endoscopy, arthroscopy, laparoscopy, ultrasound, echocardiogram.

Tufts University, Co-investigators London, Lee-Parritz, Parkison

Research Electronic Data Capture (REDCap)
Tufts CTSI offers REDCap (Research Electronic Data Capture) to investigators at Tufts CTSI and its partner institutions. REDCap is a free, secure, HIPAA-compliant, web-based application used for electronic capture and management of research and clinical study data. REDCap servers are housed in a secure local data center, behind the Tufts Medical Center firewall, and all web-based information is encrypted. The REDCap database is periodically backed up. Drs. Cheryl London (co-investigator) has undergone extensive REDCap training and is familiar with the use of this platform in the context of electronic study record reporting.

Cummings Veterinary Medical Center – Hospital for Companion animals
The equipment for evaluating companion animals for an assortment of diseases is located at the Cummings Veterinary Medical center. Imaging equipment includes digital radiography for routine imaging and contrast studies (Del Medical with Smart DR Technology), fluoroscopy (Shimadzu RS 110), ultrasonography (Philips), computed tomography (Helical-16 slice, Toshiba Aquillon) and magnetic resonance imaging (Siemens Magnetom Symphony 1.5 T). All the imaging studies can be viewed with a digital online system (PACS).

Clinical Diagnostic Laboratories
Our clinical diagnostic laboratories provide reliable, accessible, efficient and innovative laboratory diagnostic testing across multiple lab sections including Anatomical Pathology and Clinical Pathology. The labs work closely with our on-site Animal Blood Bank. We are in very close proximity of a very well equipped IDEXX laboratories section offering additional specialized testing. The collective professional expertise of the Clinical Diagnostic Laboratories at Tufts University supports the teaching, service, research and outreach missions of the, as well as veterinary practitioners and researchers. The Applied Pathology Service has an approximately Square Footage square foot of a newly renovated and sate of the art necropsy laboratory equipped with tables, necropsy implements, a band saw and all equipment needed to perform the postmortem examination including a conference room with the ability for video projection.

University of Missouri, Co-investigators Coates, McCleary-Wheeler and Henegar

Research Electronic Data Capture (REDCap) and Show Me Portal
The MU Institute for Clinical and Translational Science's (ICATS) encompasses a rich array of resources which are easily accessible to investigators. By organizing these resources into integrated clusters and cores, MU-ICATS has created a highly productive, efficient and collaborative environment for clinical and translational science. MU-ICATS has implemented three systems: REDCap, i2b2 and PowerTrials. The REDCap (Research Electronic Data Capture), created by Vanderbilt University, is a web-based application for building and managing online surveys and research databases. The i2b2 (Informatics for Integrating Biology and the Bedside) is a data warehousing system that enables researchers to use existing clinical data for discovery research. PowerTrials is a complete solution for clinical trial studies including the candidate identification during the patient care process and the management of protocol information, clinical trial initiation and enrollment activities. The MU ICATS SHOW-ME Portal provides scientists with a comprehensive toolbox of information technology resources. The portal supports the collection, analysis and sharing of information by serving as a hub for a variety of applications, from data management tools to social networking sites for scientists. REDCap (Research Electronic Data Capture) is a web application created by Vanderbilt University to facilitate data acquisition and management for a wide variety of projects, especially Institutional Review Board (IRB)-approved clinical research and basic research. Data collected in the course of the research are managed by the program and can be analyzed separately by commonly used statistical packages, including SAS, Stata, SPSS, and R. The University offers an assortment of workshops designed to help users navigate REDCap more efficiently. REDCap is a secure, web-based application for building and managing online surveys and databases. It provides automated export procedures for seamless data downloads to Excel and other common statistical programs, such as SPSS, SAS, Stata and R. REDCap also has a built-in project calendar, scheduling module, adhoc reporting tools and other advanced features, including branching logic, file uploading and calculated fields. Dr. Joan Coates (co-investigator) has undergone extensive REDCap training and is familiar with the use of this platform in the context of electronic study record reporting.

Veterinary Health Center – Small Animal Hospital (VHC-SAH)
The equipment for evaluating companion animals is located in the Veterinary Health Center (VHC). The companion dogs will be properly diagnosed and monitored for degenerative myelopathy using the imaging and

electrodiagnostic equipment as listed below. The electrodiagnostic equipment consists of a Cadwell Sierra Summit machine that contains software for electroencephalography (Cadwell Arc Alterna Amublatory EEG 32 CH), electromyography, various evoked potentials, nerve conduction studies and motor unit number estimation procedures.

Imaging equipment includes digital radiography (Ide Xplorer DR Technology) for routine radiography and contrast studies, ultrasonography (GE Logiq 9), computed tomography (Helical-64 slice, Toshiba), magnetic resonance scanner (3.0 Tesla, Titan, Toshiba), C-Arm fluoroscopy (OEC 990 Elite, GE) and CT/Positron Emission Tomography scanner (Celesteion PET/CT scanner, Toshiba). All the imaging studies can be viewed with a digital online system. Two -80 Celsius freezers and 1 refrigerator available in the VMTH for research purposes.

Veterinary Medical Diagnostic Laboratory

Necropsy procedures on the companion dogs will be performed at the Veterinary Medical Diagnostic Laboratory located adjacent to the VHC. The VMDL has a Square Footage square foot necropsy laboratory equipped with tables, necropsy implements, a band saw and all equipment needed to perform the postmortem examination. Additional digital photography equipment and a light table are available for documenting gross lesions. The laboratory has histopathology facilities and an immunohistochemistry laboratory for doing the requisite stains.

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

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Degree Type: DVM Degree Year: 2005

Attach Biographical Sketch*: File Name: Biosketch_Moore1040731165.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT12898418
Funding Opportunity Number: PAR-19-100 . Received Date: 2019-07-08T16:30:17.000-04:00

PROFILE - Senior/Key Person

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Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Coates_Biosketch1040731395.pdf

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Attach Biographical Sketch*: File Name: McClearyWheeler_NIH_Biosketch1040731517.pdf

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Attach Biographical Sketch*: File Name: BBierer_biosketch1040731571.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

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Attach Biographical Sketch*: File Name: London_Biosketch1040731407.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

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Attach Biographical Sketch*: File Name: Lee_Parritz_Biosketch1040731414.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

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Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

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Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Henegar_biosketch1040731417.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

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Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Parkison_BioSketch1040731415.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

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Credential, e.g., agency login:

Project Role*: Other (Specify) Other Project Role Category: Other Significant Contributor

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Biosketch_Bergdall1040731419.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Jessica Middle Name Last Name*: Evans Suffix:

Position/Title*: Program Manager
Organization Name*: The Ohio State University
Department: Responsible Research Practices
Division: Office of Research
Street1*: 1960 Kenny Rd
Street2:
City*: Columbus
County:
State*: OH: Ohio
Province:
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Credential, e.g., agency login:

Project Role*: Other (Specify) Other Project Role Category: Other Significant Contributor

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Biosketch_Evans1040731447.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Sarah A Moore

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Associate professor, Neurology and Neurosurgery

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Auburn University (Auburn, AL)	DVM	May 2005	Veterinary Medicine
University of Missouri (Columbia, MO)	Internship	June 2006	Medicine and Surgery
North Carolina State University (Raleigh, NC)	Residency	July 2009	Neurology and Neurosurgery
The Ohio State University (Columbus, OH)	Research Fellowship	Sept 2011	Spinal cord injury

A. **Personal Statement**

I am the program director for the OSU CTSA's Comparative and Translational Medicine (CTM) Optional Module, and am an Associate Professor in the department of Veterinary Clinical Sciences at OSU with a research focus in dog models of spinal cord disease. The focus of the CTM is to grow the integration of veterinary clinical trials into the translational research pipeline in order to improve efficiency in therapeutic development. I am also a board-certified veterinary neurologist and neurosurgeon by training, and have over ten years of experience conducting veterinary clinical trials as a translational research strategy. As the PI on the proposed work, I am well-positioned to lead the collaborative SMART IACUC effort at the national level. Locally, I have served since 2017 as the chair of our IACUC privately owned animals subcommittee, which functions as our veterinary medical center's (VMC) IRB for veterinary clinical research. In this role, I have developed and implemented an improved review process for veterinary clinical research at our institution, working in close collaboration with other members of the current study team to do so (London, O'Meara, Bergdall). Our group has also worked locally to implement a standardized process for reporting and review of serious adverse events in VMC clinical trials; work with principal investigators across our college to improve understanding of approval processes for animal studies; develop a revised clinical trial consent template to facilitate a uniform and robust consent process in our hospital; and establish strong relationships with institutional regulatory bodies, including the IACUC and IRB, to facilitate an open dialogue on improving veterinary clinical research practices. This local work has served as an example for other institutions and we have collaborated with both Tufts (London, Lee-Parritz) and Missouri (Coates, Henegar) to develop harmonized processes. Nationally, I am a member of the CTSA One Health Alliance (COHA) Clinical Studies Subcommittee (along with Coates, London, and McCleary-Wheeler) and COHA One Health Datasets working group both of which focus on integrating natural animal models of disease into the translational research process. Lastly, I am a founding member and current leader of a group of veterinary spinal surgeons, human physicians, and basic science researchers focused on dog models of SCI as translational tools to improve health outcomes in people (CANSORT-SCI). This role as an international consortium leader has given me unique perspective on cross-institutional relationships and agreements that can ease the conduct of multi-site clinical research. I am co-PI on an active R21 (Coates and Moore) from NCATS which focuses on developing a veterinary platform trial for canine degenerative myelopathy (a spontaneous large animal model of ALS) to facilitate translational efficiency in drug development for neurodegenerative diseases. This effort has provided

me further experience navigating the unique ethical and regulatory challenges inherent to veterinary clinical trials and has provided me the background and collaborative relationships across COHA network institutions to help meet those challenges.

B. Positions and Honors

Employment
September 2009- September 2011; Post-doctoral research fellow, Department of Veterinary Biosciences, The Ohio State University, Columbus OH. Focus on Neuroinflammation. Mentor Dr. Michael Oglesbee.

September 2009-June 2015; Assistant Professor, Neurology and Neurosurgery, Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, OH.

June 2015- Present; Associate Professor with tenure, Neurology and Neurosurgery, Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, OH

November 2017- Present; Chair, privately owned animals subcommittee of The Ohio State University Institutional Animal Care and Use Committee. The Ohio State University, Columbus, OH.

October 2018- Present; Director, Comparative and Translational Medicine Program. Center for Clinical and Translational Sciences, The Ohio State University, Columbus, OH

C. Contributions to Science

1. Building multi-institutional collaborative networks to study clinical dog models of neurologic disease. Experimental models of neurologic diseases such as ALS and traumatic spinal cord injury have been vital to define mechanisms of disease and for early-stage drug development. However, translational efficiency from the laboratory to the clinical setting has been historically poor. Spontaneous animal models of disease can serve as clinical models that bridge laboratory and clinical studies and can provide important second-species confirmation of treatment effects to enhance likelihood of translational success. To this end, I have worked with colleagues in my field to develop the Canine Consortium of Spinal Cord Injury Researchers (CANSORT-SCI), a group of veterinary spinal surgeons, human physicians, basic science researchers, and industry partners. While this group focuses specifically on the clinical dog model of traumatic spinal cord injury, experience gained from the development of this group including clinical trial design and developing standardized outcome assessments, can be applied to the canine DM collaborative network as well. I am experienced in using REDcap software to design data collection instruments for veterinary clinical studies and am the primary developer of the International Canine Spinal Cord Injury Registry currently in use by 8 veterinary institutions in the United States and Europe to capture longitudinal data in dogs with SCI. The following articles represent multi-institutional collaborative works focusing on canine clinical models of neurologic disease:

a) Targeting translational successes through CANSORT-SCI: using pet dogs to identify effective treatments for spinal cord injury. Moore SA, Granger N, Olby NJ, et al. *Journal of Neurotrauma*, 2017. DOI: 10.1089/neu.2016.4745. PMID: 28230415.

b) Clinical characteristics of canine fibrocartilaginous embolic myelopathy (FCE): a systematic review of 393 cases (1973-2013). Bartholomew KA, Stover KE, Olby NJ, Moore SA. *Veterinary Record*, 2016; 179 (25). PMID: 27682506.

c) Development of an International Canine Spinal Cord Injury (CSCI) observational registry: a collaborative veterinary data-sharing network to optimize translational studies of SCI. **Moore SA**, Zidan N, Spitzbarth I, Nout-Lomas YS, Granger, N, da Costa RC, et al. *Spinal Cord*, 2018; 56: 656-665.

2. Developing quantitative outcome measures in dog models of spinal cord disease. While rodent models are pivotal in establishing mechanism and in early stage drug development, lack of translational

efficiency has recently highlighted the need for more robust animal models of SCI that better resemble the human condition. In deed recent focus has turned to dog models of certain types of SCI, for which there is a need for validated quantitative outcome measures. My lab has focused on developing, validating, and translating in to routine use several outcome measures of canine SCI including a simplified method of walking track analysis**,** and methods of quantitative sensory testing**.** Our laboratory has also recently adapted the Basso-Beattie-Bresnahan locomotor rating scale for use in dogs which allows investigators doing dog work to speak the same language as those doing rodent work as well as allows for use in dogs the most reliable locomotor scale published to date in rats. The articles below represent studies focused on developing quantitative outcome measure for clinical use in dogs with spinal cord disease:

a) Adaptation of the Basso-Beattie-Bresnahan locomotor rating scale for use in a clinical model of spinal cord injury in dogs. Song RB, Basso DM, da Costa RC, Fisher LC, Mo X, Moore SA. Journal of Neuroscience Methods, 2016; 268. PMID: 27155106.

b) A simplified method of walking track analysis to assess short-term locomotor recovery after acute spinal cord injury caused by thoracolumbar intervertebral disc extrusion in dogs. Song RB, Basso DM, da Costa RC, Fisher LC, Mo X, Moore SA. The Veterinary Journal, 2016; 210. PMID: 26900008.

c) von Frey anesthesiometry to assess sensory impairment after acute spinal cord injury caused by thoracolumbar intervertebral disc extrusion in dogs. Song RB, Basso DM, da Costa RC, Fisher LC, Mo X, Moore SA. The Veterinary Journal, 2016; 209. PMID: 26832808.

d) The use of an electronic von Frey device for evaluation of sensory threshold in neurologically normal dogs and those with acute spinal cord injury. Moore SA, Hettlich BF, Waln A. The Veterinary Journal, 2013; 197. PMID: 23246235.

3. Defining ependymal cell responses in naturally occurring spinal disease in pet dogs. Spinal cord ependymal (SEL) cells are of recent interest to neuroscience researchers because of their ability to regenerate after CNS injury, and indications that they may function as endogenous neural stem cells to repair the injured spinal cord. In rodent models of SCI, cells of the SEL differentiate in to astrocytes, neurons, and oligodendroglia after injury and migrate to the lesion epicenter to assist with tissue repair. The ultimate goal would be to manipulate endogenous stem cell function of these cells to circumvent feasibility and ethical issues associated with the use of exogenous cell-based therapies. Pet dogs have a high incidence of naturally occurring SCI which can serve as a pre-clinical model to confirm and extend laboratory findings related to tissue regeneration and repair after SCI. We started by characterizing the tissues responses with in the SEL, and a specialized cluster of ependymal cells called the choroid plexus, after naturally occurring SCI in dogs. First, we investigated the choroid plexus as a potential effector of global inflammatory responses that may inhibit tissue repair. We found that the choroid plexus serves as an important source of pro-inflammatory cytokines such as TNF, IL-1β, and heat shock proteins after SCI. Because of the proximity to the cerebrospinal fluid, these responses have the potential to exert global effects after injury and potential a diffuse pro-inflammatory state within the neuraxis. Additionally, this may serve to inhibit the neural stem cell niche within and around the spinal cord central canal and the spinal ependymal layer. Next we evaluated the morphology of the normal canine SEL and compared these findings to the SEL of dogs with SCI. We found strong similarities between the canine and human SEL, and observed increases in SEL cell numbers after injury indicating a possible proliferative response. Additionally, GFAP staining was increased in the SEL after injury, indicating that cells of the canine SEL take on a neural stem cell phenotype and may contribute to tissue repair and regeneration. We are currently comparing SEL responses across several injury types, including traumatic, ischemic and neurodegenerative SCI models**.** This will allow a better understanding of SEL responses to tissue injury and will highlight clinical disease models that will be likely to benefit from therapies that augment SEL proliferation and function.

a) Spinal ependymal responses to naturally occurring traumatic spinal cord injury in dogs. Moore SA, Oglesbee MJ. Veterinary Pathology, 2016; 52. PMID: 25445323.

b) Quantitative assessment of hsp70, IL-1β and TNF-α in the spinal cord of dogs with E40K SOD1-associated degenerative myelopathy. Lovett MC, Coates JR, Shu Y, Oglesbee MJ, Fenner W, Moore SA. The Veterinary Journal, 2014; 200. PMID: 24662024

c) Involvement of the choroid plexus in the inflammatory response after acute spinal cord injury in dogs: an immunohistochemical study. Moore SA, Oglesbee MJ. Veterinary Immunology and Immunopathology, 2012; 148. PMID: 22840733

D. Research Support (last 3 years)

A platform trial design to accelerate translational therapies in a canine disease model of ALS
PI: Coates JR, Moore SA Co-I: Olby NJ, Faissler D.
Source: NIH-NCATS R21, Period: 7/2018-5/2020. The goal of this project is to develop a multi-institutional collaborative network to facilitate translational ALS therapeutic development using a spontaneously occurring canine model of ALS.

Identifying and treating neuropathic pain in dogs with syringomyelia.
PI: Moore SA Co-I: Cole L, Hostnik ET, Hechler A
Source: Private Source Period: 5/2017- 4/2019. The goal of this study is to further develop a spontaneous canine model of neuropathic pain by correlating the results of quantitative sensory testing with MRI findings in dogs with syringomyelia. This study will also evaluate efficacy of a novel neuropathic pain drug.

Diagnosing and managing neuropathic pain in dogs with spinal cord injury.
PI: Sarah Moore. Co-I Ronaldo da Costa, Laurie Cook, Austin Kerns.
Source: OSU Canine Research Funds, Period: 1/2016-12/2017. The major goal of this study is to provide a long term evaluation of the incidence of neuropathic pain in dogs with chronic spinal cord injury.

Consortium for the advancement of Neuromusculoskeletal Science and Locomotion.
PI: Alicia Berton. Co-I**: Sarah Moore,** Nina Kieves, Stephen Jones, Sushmitha Durgam.
Source: OSU College of Veterinary Medicine Signature Programs, Period: 2016-2019. The major goal of this project is to establish a college-wide signature program in neuromusculoskeletal research to enhance translational studies in all areas of neuromusculoskeletal repair, regeneration, and recovery.

Neuropathic pain in a canine spontaneous model of osteoarthritis.
PI: Nina Kieves. Co-I: **Sarah Moore**, Turi Aarnes.
Source: OSU Canine Research Funds, Period: 1/2016-12/2018. The goal of this project is to evaluate prevalence of, and the effect of regional anesthetics on, the development of neuropathic pain in a spontaneous dog model of osteoarthritis.

AAV9-mediated SOD1 down-regulation: Gene therapy for degenerative myelopathy.
Co-PIs: Brian Kaspar and Sarah Moore. Co-I Shibi Likhite, David Arnold.
Source: Private Source Period 12/2015-11/2018. The major goal of this project is to evaluate the safety and feasibility of a gene therapy treatment in canine degenerative myelopathy, a naturally occurring model of familial ALS.

Diagnosing and managing neuropathic pain in dogs with spinal cord injury.
PI: Sarah Moore.
Source: Private Source Period 6/2015-5/2017. The major goal of this study is to assess inter-rater reliability of a technique for quantitative sensory testing (QST) in dogs and to assess the effects of gabapentin on QST in normal dogs.

Characterizing clinical and cellular responses in dogs with fibrocartilagenous embolism.
PI: Sarah Moore. Source: Private Source Period 5/2014-4/2016. The major goal of this project is to characterize the clinical and cellular responses within the spinal cord of dogs with FCE, a spontaneous model of ischemic myelopathy in people.

OMB No. 0925-0001 and 0925-002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: COATES, Joan Ripley

eRA COMMONS USER NAME (agency login): eRA Commons User Name

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Missouri, Columbia	BS	05/1987	General Agriculture (magna cum laude)
University of Missouri, Columbia, MO	DVM	05/1990	Veterinary Medicine (magna cum laude)
Auburn University, Auburn, AL	MS	05/1994	Neuroscience
Texas A&M University, College Station, TX	Intern	07/1991	Rotating Internship Small Animal Medicine and Surgery
Auburn University, Auburn , AL	Resident	07/1994	Neurology & Neurosurgery

A. Personal Statement

I am a board-certified veterinary neurologist with neurosurgical expertise. One of the rewards of my veterinary medical research is having the opportunity to play such an integral role in advancing medicine through the discovery of animal models of human disease and the development of therapeutic approaches with potential applicability in human disease. My research focus for over 18 years as a principal investigator has been on canine degenerative myelopathy (DM) associated with a *SOD1* mutation, which was discovered by our group in 2009 and serves as a canine disease model of amyotrophic lateral sclerosis (ALS) (review key articles below). The homogeneity of phenotype and disease progression provide a unique opportunity to gain further insight into the underlying disease mechanisms of ALS and into the identification of reliable biomarkers for monitoring effects on disease progression to therapeutic approaches. I have guided investigations of clinically applicable biomarkers that may facilitate prospective studies of canine DM as a disease model on which therapeutic approaches can be evaluated for patients with ALS. I additionally conduct clinical trial research for preclinical studies on canine DM with studies in immunization, antisense oligonucleotide, and gene therapies. In addition to the canine DM studies, I have served as the lead veterinary neurology/neurosurgery collaborator in the studies of the CLN2 canine model of Batten disease. I was involved in the initial studies that characterized the disease phenotype and therapeutic interventions. These studies subsequently led to preclinical studies in TPP1 enzyme replacement and AVV gene therapies that are being administered to affected children.

With respect to my personal interest on this grant application, I will serve as a Co-I who will collaborate with the MU IACUC and oncology colleagues to provide input for and implement a universal IACUC. The SMART IACUC will serve to develop a platform designed to ease common challenges associated with initiating multi-site clinical research. The University of Missouri (MU) works in partnership with the Washington University in St. Louis CTSA parent grant. The goal in collaboration across additional CTSA sites (OSU, Tufts University) with veterinary academic centers is to optimize a set of standard operating procedures for clinical trial research. By developing a SMART IACUC, impediments associated with accessing centers for relevant caseload will be reduced.

1. Coates JR, March PA, Oglesbee M, Ruaux CG, Olby NJ, Berghaus RD, O'Brien DP, Keating JH, Johnson GS, Williams DA. Clinical characterization of a familial degenerative myelopathy in Pembroke Welsh Corgi dogs. J Vet Intern Med. 2007 Nov-Dec;21(6):1323-31. PMID: 18196743.
2. Awano T, Johnson GS, Wade CM, Katz ML, Johnson GC, Taylor JF, Perloski M, Biagi T, Baranowska I, Long S, March PA, Olby NJ, Shelton GD, Khan S, O'Brien DP, Lindblad-Toh K, Coates JR. Genome-wide association analysis reveals a SOD1 mutation in canine degenerative myelopathy that resembles

amyotrophic lateral sclerosis. Proc Natl Acad Sci U S A. 2009 Feb 24;106(8):2794-9. PMID: 19188595; PMCID: PMC2634802.
3. March PA, Coates JR, Abyad RJ, Williams DA, O'Brien DP, Olby NJ, Keating JH, Oglesbee M. Degenerative myelopathy in 18 Pembroke Welsh Corgi dogs. Vet Pathol. 2009 Mar;46(2):241-50. PMID: 19261635.
4. Coates JR, Wininger FA. Canine degenerative myelopathy. Vet Clin North Am Small Anim Pract. 2010 Sep;40(5):929-50. PMID: 20732599.

B. Positions and Honors

Positions and Employment

1990 - 1991	Intern, Texas A&M University, Department of Small Animal Medicine and Surgery, College Station, TX
1991 - 1994	Resident, Auburn University, Department of Small Animal Surgery and Medicine, Auburn, AL
1994 - 1997	Assistant Professor, University of Georgia, Department of Small Animal Medicine and Surgery, Athens, GA
1997 - 2003	Assistant Professor, Texas A&M University, Department of Small Animal Medicine and Surgery, College Station, TX
1997 - 2003	Director of Neurology & Neurosurgery Service, Texas A&M University, Veterinary Medical Teaching Hospital, College Station, TX
2003 - 2011	Associate Professor, University of Missouri, Department of Veterinary Medicine and Surgery, Columbia, MO
2005 - present	Service Leader of Neurology & Neurosurgery Service, University of Missouri, Veterinary Medical Teaching Hospital, Columbia, MO;
2011 - present	Professor, University of Missouri, Department of Veterinary Medicine and Surgery, Columbia, MO
2018-present	Section Head of Neurology & Neurosurgery, Department of Veterinary Medicine and Surgery, Columbia, MO
2018-present	Residency Program Director, Neurology & Neurosurgery, University of Missouri and Charlotte Animal Referral Emergency (MU-CARE)
2018-present	MU Executive Committee Interdisciplinary Neuroscience Program

Honors and Memberships

1990-present	Member, American Veterinary Medical Association
1991	Waddell Scholarship Award, Texas Veterinary Medical Foundation
1993	Outstanding Master of Science Student, Auburn University
1994-present	Specialty Board Certification in Neurology, American College of Veterinary Internal Medicine
1994-present	Member, American College of Veterinary Internal Medicine (ACVIM)
2000	Clinical Service Award, Texas A&M Medical Teaching Hospital
2003-present	Member of the Missouri Veterinary Medical Association
2004	New Faculty Teaching Scholar, University of Missouri
2009	Hero in Medicine Award, American College of Veterinary Internal Medicine
2009	Pfizer Award for Research Excellence, University of Missouri College of Veterinary Medicine
2011-2014	Elected Secretary for the ACVIM Specialty of Neurology
2013-present	Board of Directors, Veterinary Specialists Outreach and Awareness Project (VetSOAP)
2015	Recognition of Research Excellence, American Boxer Charitable Foundation
2019	Recipient of the MU College of Veterinary Medicine Dean's Impact Award

C. Contribution to Science

1. Canine degenerative myelopathy (DM) is an adult-onset disease in dogs that leads to paralysis and eventual death. Canine DM has many similarities to familial SOD1-associated ALS, based on a naturally occurring SOD1 mutation. Often when the pet owner makes a decision for humane euthanasia of their pet, they want to have the tissues donated for DM and ALS research. We can capture the disease pathologies at varying disease severities that may serve to document the multifactorial pathogenesis shared between

ALS and DM. The articles below represent collaborative pathologic studies in SOD1, neuroinflammation and neurofilament accumulation.

a. Crisp MJ, Beckett J, Coates JR, Miller TM. Canine degenerative myelopathy: biochemical characterization of superoxide dismutase 1 in the first naturally occurring non-human amyotrophic lateral sclerosis model. Exp Neurol. 2013 Oct;248:1-9. PMCID: PMC3773294.

b. Lovett MC, Coates JR, Oglesbee M, Fenner W, Moore SA. Quantitative assessment of HSP70, IL-1β and TNF-α in the spinal cord of dogs with E40K *SOD1*-associated degenerative myelopathy. The Veterinary Journal. 2014; 200(2):312-317.

c. Toedebusch CM, Bachrach M, Garcia VB, Johnson GC, Shaw GPJ, Coates JR, Garcia ML. Cerebrospinal fluid phosphorylated neurofilament heavy (pNF-H) as a diagnostic marker of canine degenerative myelopathy. J Vet Int Med. 2017;31:513-520. PMID 28186658.

d. Fernandez-Trapero M, Espejo-Porras, F, Coates JR, Perez-Diaz C, de Lago E, Fernandez-Ruiz J. Up-regulation of CB2 receptors in reactive astrocytes in canine degenerative myelopathy, a disease model of amyotrophic lateral sclerosis. Disease Models & Mechanisms. 2017;10:5551-558. PMID: 28069688.

2. Canine degenerative myelopathy phenotype has similarities to familial SOD1-associated ALS and recapitulates the clinical progression to upper motor neuron onset ALS. In addition to the contributions above, with a team of collaborators, we have continued to develop canine degenerative myelopathy as a disease model by further investigations of the lower motor neuron pathology. Similarities between the canine and human nervous systems and the homogeneity in onset and clinical progression of canine DM will facilitate translation of therapies.

a. Shelton GD, Johnson GC, O'Brien DP, Katz ML, Pesayco JP, Chang BJ, Mizisin AP, Coates JR. Degenerative myelopathy associated with a missense mutation in the superoxide dismutase 1 (SOD1) gene progresses to peripheral neuropathy in Pembroke Welsh corgis and boxers. J Neurol Sci. 2012 Jul 15;318(1-2):55-64.

b. Morgan BR, Coates JR, Johnson GC, Bujnak AC, Katz ML. Characterization of intercostal muscle pathology in canine degenerative myelopathy: a disease model for amyotrophic lateral sclerosis. J Neurosci Res. 2013 Dec;91(12):1639-50. PMCID: PMC4096151.

c. Morgan BR, Coates JR, Johnson GC, Shelton GD, Katz ML. Characterization of thoracic motor and sensory neurons and spinal nerve roots in canine degenerative myelopathy, a potential disease model of amyotrophic lateral sclerosis. J Neurosci Res. 2014 Apr;92(4):531-41. PMCID: PMC4096142.

d. Katz ML, Jensen CA, Student JT, Johnson GC, Coates JR. Cervical spinal cord and motor unit pathology in a canine model of SOD1-associated amyotrophic lateral sclerosis. Journal of Neurological Sciences 2017;378:193-203.

3. Once the *SOD1* mutation was established as a major underlying cause of canine degenerative myelopathy, we continued to study the mutation in the canine population. We established a second mutation in the Bernese Mountain Dogs. Moreover, we provided a broader view of the potential contribution of known *SOD1* missense mutations across multiple breeds and concluded that the E40K mutant SOD1 is widespread and common among companion dogs. Recently, we also described a genetic modifier of neuroinflammation affecting risk of Pembroke Welsh Corgis homozygous for the E40K SOD1 mutation.

a. Wininger FA, Zeng R, Johnson GS, Katz ML, Johnson GC, Bush WW, Jarboe JM, Coates JR. Degenerative myelopathy in a Bernese Mountain Dog with a novel SOD1 missense mutation. J Vet Intern Med. 2011 Sep-Oct;25(5):1166-70.

b. Zeng R, Coates JR, Johnson GC, Hansen L, Awano T, Kolicheski A, Ivansson E, Perloski M, Lindblad-Toh K, O'Brien DP, Guo J, Katz ML, Johnson GS. Breed distribution of SOD1 alleles previously associated with canine degenerative myelopathy. J Vet Intern Med. 2014 Mar-Apr;28(2):515-21. PMCID: PMC4238831.

c. Ivansson EL, Megquier K, Kozyrev SV, Muren E, Baranowska-Korberg I, Sofford R, Koltookian M, Tonomura N, Zeng R, Kolicheski AL, Hansen L, Katz ML, Johnson GC, Johnson GS, Coates JR, Lindblad-Toh K. Variants within the SP110 nuclear body protein modify risk of canine degenerative myelopathy. Proceed Natl Acad Sci USA. 2016;113(22):E3091-3100 PMCID: PMC4896683.

4. I am involved with the Comparative Neurology Program of the College of Veterinary Medicine at the University of Missouri. We focus our research efforts in comparative and translational medicine. I have served as a collaborator in studies that identified and characterized the Dachshund CLN2 disease model with a spontaneous null mutation in TPP1. The publications define the neurologic, cognitive and ophthalmic phenotypes in CLN2 dogs that show similarities to children affected by this disorder.
   a. Awano T, Katz ML, O'Brien DP, Sohar I, Lobel P, Coates JR, Khan S, Johnson GC, Giger U, Johnson GS. A frame shift mutation in canine TPP1 (the ortholog of human CLN2) in a juvenile Dachshund with neuronal ceroid lipofuscinosis. Mol Genet Metab. 2006 Nov;89(3):254-60.
   b. Sanders DN, Kanazono S, Wininger FA, Whiting RE, Flournoy CA, Coates JR, Castaner LJ, O'Brien DP, Katz ML. A reversal learning task detects cognitive deficits in a Dachshund model of late-infantile neuronal ceroid lipofuscinosis. Genes Brain Behav. 2011 Oct;10(7):798-804. PMCID: PMC3190059.
   c. Whiting RE, Narfström K, Yao G, Pearce JW, Coates JR, Castaner LJ, Katz ML. Pupillary light reflex deficits in a canine model of late infantile neuronal ceroid lipofuscinosis. Exp Eye Res. 2013 Nov;116:402-10. PMCID: PMC3845481.
   d. Katz ML, Johnson GC, Leach SB, Williamson BG, Coates JR, Whiting REH, Vansteenkiste DP, Whitney MS. Extra-neuronal pathology in a canine model of CLN2 Neuronal Ceroid Lipofuscinosis after intracerebroventricular gene therapy that delays neurologic disease progression. *Gene Therapy*, 2017;24(4):215-233.

5. With the Dachshund CLN2 disease model, we can develop therapeutic interventions that would delay disease onset and attenuate the progression of the clinical signs. The publications below represent our work on therapeutic approaches of administering recombinant human TPP1 to the brain.
   a. Vuillemenot BR, Katz ML, Coates JR, Kennedy D, Tiger P, Kanazono S, Lobel P, Sohar I, Xu S, Cahayag R, Keve S, Koren E, Bunting S, Tsuruda LS, O'Neill CA. Intrathecal tripeptidyl-peptidase 1 reduces lysosomal storage in a canine model of late infantile neuronal ceroid lipofuscinosis. Mol Genet Metab. 2011 Nov;104(3):325-37.
   b. Katz ML, Coates JR, Sibigtroth CM, Taylor JD, Carpentier M, Young WM, Wininger FA, Kennedy D, Vuillemenot BR, O'Neill CA. Enzyme replacement therapy attenuates disease progression in a canine model of late-infantile neuronal ceroid lipofuscinosis (CLN2 disease). J Neurosci Res. 2014 Nov;92(11):1591-8. PMCID: PMC4263309.
   c. Vuillemenot BR, Kennedy D, Cooper JD, Wong AM, Sri S, Doeleman T, Katz ML, Coates JR, Johnson GC, Reed RP, Adams EL, Butt MT, Musson DG, Henshaw J, Keve S, Cahayag R, Tsuruda LS, O'Neill CA. Nonclinical evaluation of CNS-administered TPP1 enzyme replacement in canine CLN2 neuronal ceroid lipofuscinosis. Mol Genet Metab. 2015 Feb;114(2):281-93.
   d. Katz ML, Tecedor L, Chen Y, Williamson BG, Lysenko E, Wininger FA, Young WM, Johnson GC, Whiting REH, Coates JR, Davidson BL. AAV-mediated transduction of ventricular lining cells delays neurodegenerative disease onset and progression in a canine model of the late infantile form of Batten disease. Sci Transl Med. 2015;7(313) 313ra180-313ra180 1-10, 2015. PMCID: PMC4968409.

Complete list of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/joan.coates.1/bibliography/44187568/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

Private Source — Coates and Katz (CoPIs) — 06/01/2019 – 05/31/2021
Characterization of sensory neuronal and muscle pathology in canine degenerative myelopathy to identify targets for therapeutic intervention
This project will histopathologically explore the sensory neuronal pathway to determine the earliest site for disease onset.

1R21TR002277 — Coates and Moore (CoPIs) — 07/01/2018 – 06/30/2020
National Institutes of Health

A Platform Trial Design to Accelerate Translational Therapies in a Canine Disease Model of ALS. National Institutes of Health. 07/01/2018–05/31/2020.
By correlating the development of sensory neuron and muscle pathology, we will be able to determine whether these pathologies occur prior to or independently of other pathology in the associated motor and sensory neurons for better understanding of neurodegeneration in DM.

R21NS103028 Lorson (PI); Coates (Co-I) 04/01/2018-03/31/2019
National Institutes of Health
IGHMBP2 patient-derived missense mutations: large animal models of SMARD1
The major goals of this project are to develop important models of Spinal Muscular Atrophy with Respiratory Distress Type I (SMARD1) that will shed light upon the underlying function responsible for disease development as well as provide a valuable disease context to develop novel SMARD1 therapeutics.

Private Source Coates (PI) 01/01/2015–12/31/2019
Biomarker Development in Canine Degenerative Myelopathy for Diagnosis and Longitudinal Monitoring of a Therapeutic Approach
The major goal is to longitudinal evaluate canine degenerative myelopathy through study of CSF (pNF-H), MRI and electrophysiology.

1R01EY023968-01A1 Katz (PI); Coates (Co-I) 09/01/2014–08/31/2019
National Eye Institute/NIH
Prevention of Retinal Degeneration by Transgenic Autologous Stem Cells
The major goal is to limit retinal blindness in a canine disease model of neuronal ceroid lipofuncinosis (CLN2) using transgenic autologous stem cells

Private Source Coates and Sah (Co-PIs) 09/01/2015–08/31/2019
TREAT ALS Drug Development Contract
Development of an AAV Gene Therapy Targeting SOD1 for the Treatment of ALS – Translation of Delivery
The major goal is to evaluate a gene therapy approach on canine DM for translation to ALS.

Private Source Coates and Gerdes (Co-PIs) 03/01/2016–08/31/2020
Private Source
Temporal Regional PET Imaging of the CNS EAAT2 Protein in Canine Degenerative Myelopathy as a Disease Model of ALS
The major goal is to use PET/CT imaging for a radionuclide to longitudinally monitor canine degenerative myelopathy.

Selected Completed Research Support

Coates and Katz (Co-PIs) 10/01/2014–09/30/2017
Spinal Cord Injury Research Program, University of Missouri System
Disease Mechanisms in a Canine Model of Amyotrophic Lateral Sclerosis
The major goal is to evaluate canine degenerative myelopathy tissues to develop a better understanding of the LMN disease pathology in ALS.

R21 NS078242-02 Coates (PI) 09/26/2012–09/30/2017
National Institute of Neurological Disorders and Stroke (NINDS)
Therapeutic Development for Amyotrophic Lateral Sclerosis in a Canine Model
The major goal is to evaluate an antisense oligonucleotide therapy in treatment of canine degenerative myelopathy.

Private Source Coates and Robertson (Co-PIs) 09/01/2013–08/31/2015
Private Source
Immunization Therapy in a Canine Disease Model of ALS
The major goal was to evaluate immunization therapy in canine degenerative myelopathy, which serves as a model of amyotrophic lateral sclerosis (ALS).

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Angela McCleary-Wheeler

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Assistant Professor, Section of Medical Oncology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Iowa State University, Ames, Iowa	B.S.	05/2001	Biochemistry
Iowa State University, Ames, Iowa	D.V.M.	05/2005	Veterinary Medicine
University of Missouri, Columbia, MO		06/2006	Small Animal Medicine/ Surgery Internship
North Carolina State University, Raleigh, NC		07/2009	Medical Oncology Residency
Mayo Clinic, Rochester, MN	Ph.D.	02/2014	Biochemistry/Molecular Biology

A. Personal Statement

The goals of my research are twofold: 1. To advance our understanding of mechanisms governing gene transcription in cancer biology; and 2. To utilize what is learned to better prognosticate cancer types as well as to aid in the development of novel, targeted cancer therapeutics using a comparative cancer model system. Specifically, my research interests focus on uncovering the mechanisms of permissive gene transcription in the context of epigenetic alterations. Projects in my laboratory include studies evaluating the intersection of signaling pathways, such as SHIP and Hedgehog signaling, and chromatin modifying enzymes in cancer. My laboratory seeks to describe and understand the molecular mechanisms governing the activity of transcription factors in cancers with an interest specifically in osteosarcoma and hematologic malignancies. The translational aspect of my research is driven by my dual training as both a basic scientist and a veterinary oncologist. I have had the opportunity to be involved in clinical research that includes biomarker studies as well as clinical trials involving veterinary patients. Because companion animals are afflicted by spontaneously-arising malignancies, many of which have high conservation in the biology, progression, and therapeutic response to their human disease counterparts, they can serve as highly relevant models of spontaneous tumor study. This unique opportunity has further inspired my interest to pursue comparative cancer models through the investigation of spontaneous companion animal tumors. Using translational and comparative studies, a goal of more applied and accelerated cancer diagnostics and therapeutics can be achieved for both humans and animals. Improving clinical trial infrastructure and resources across institutions to promote the conduct of high-quality, multi-institutional trials in veterinary patients is paramount to success in this area of translational research.

Publications relevant to this proposal include:

a) Villarnovo D, **McCleary-Wheeler AL**, Richards KL. Barking up the right tree: Advancing our understanding and treatment of lymphoma with a spontaneous canine model. *Curr Opin Hematol*. 2017 Apr 19;24:000-000. PMID: 28426554

b) Zheng X, Vittar NB, Gai X, Fernandez-Barrena MG, Moser CD, Hu C, Almada LL, **McCleary-Wheeler AL,** Elsawa SF, Vrabel AM, Shire AM, Comba A, Thorgeirsson SS, Kim Y, Liu Q, Fernandez-Zapico ME, Roberts LR. The transcription factor GLI1 mediates TGF-β1 driven EMT in hepatocellular carcinoma via a SNAI1-dependent mechanism. *PLoS One*. 2012 7(11):e49581. PMC3501480

c) **McCleary-Wheeler AL**, Lomberk GA, Weiss FU, Schneider G, Fabbri M, Poshusta TL, Dusetti NJ, Baumgart S, Iovanna JL, Ellenrieder V, Urrutia R, Fernandez-Zapico ME. Insights into epigenetic mechanisms controlling pancreatic carcinogenesis. *Cancer Lett.* 2013 Jan 28;328(2):212-21. PMC3513548

d) Liu L, Xu H, Wang W, Wu C, Chen Y, Yang J, Cen P, Xu J, Liu C, Long J, Guha S, Fu D, Ni Q, Jatoi A, Chari S, **McCleary-Wheeler AL**, Fernandez-Zapico ME, Li M, Yu X. A preoperative serum signature of CEA+/CA125+/CA19-9 ≥ 1000 U/mL indicates poor outcome to pancreatectomy for pancreatic cancer. *Int J Cancer*. 2015 May 1;136(9):2216-27. PMC25273947

B. Positions and Honors

Positions and Employment

2018-Current Assistant Professor, Department of Veterinary Medicine and Surgery, University of Missouri, Columbia, MO
2014-2018 Assistant Professor, Department of Clinical Sciences, Cornell University, Ithaca, NY
2014-Current Adjunct Professor, Department of Biomedical Sciences, Cornell University, Ithaca, NY

Other Experience and Professional Memberships

2005-Current Member, American Veterinary Medical Association
2011-Current Member, American College of Veterinary Internal Medicine
2013-Current *ad hoc* reviewer, *PLoS One*
2014-Current Member, Veterinary Cancer Society
2014-Current Active Member, American Association for Cancer Research
2014- Current *ad hoc* reviewer, *Journal of Veterinary Internal Medicine*
2014-2018 Program Director, Cornell University Hospital for Animals Medical Oncology Residency Program
2015-2018 Member, ACVIM Oncology Specialty Exam Writing Committee
2018-Current Member, ACVIM Forms for Residency Training Task Force Committee
2018-Current Steering Committee Member, Clinical and Translational Science Award One Health Alliance

C. Contribution to Science

1. Evaluation of noninvasive methods for earlier detection of canine urinary bladder transitional cell carcinoma. Canine urinary bladder transitional cell carcinoma has a poor prognosis with a median survival times of 9-10 months even with the most effective, currently known treatment options. One reason for this is late disease detection. Clinical signs associated with this tumor mimic other more common, nonmalignant conditions, such as urinary tract infections and bladder calculi. This suggests earlier detection may help improve outcomes. Many noninvasive detection methods have proven to lack sensitivity and specificity. Based upon data published in human urinary bladder transitional cell carcinoma, we sought to evaluate active telomerase as assayed via a PCR-based method from the urine of normal dogs, dogs with non-malignant lower urinary tract disease, and dogs diagnosed with transitional cell carcinoma. Initial evaluation suggested this detection of active telomerase in urine identifies canine urinary bladder transitional cell carcinoma, with limited false-positive detection. I was involved with study conception and designed, performed the experiments, and wrote the manuscript. Others are continuing this research to further determine sensitivity and specificity of the assay and optimize its use to further define clinical utility.

a) **McCleary-Wheeler AL**, Williams LE, Hess PR, Suter SE. Evaluation of an in vitro telomeric repeat amplification protocol assay to detect telomerase activity in canine urine. *Am J Vet Res* 2010 Dec;71(12):1468-1474. PMID: 21117999

2. Effects of histone deacetylase inhibition on bone density. Histone deacetylase inhibitors are used to treat epilepsy and are increasingly being explored and used for the treatment of various cancers. Histone deacetylase enzymes are important for normal bone development, but there was no prior work to establish the role inhibitors of these enzymes have on the skeletal system. Using the histone deacetylase inhibitor vorinostat, we evaluated the effect on bone remodeling. We found that treatment of mice with vorinostat resulted in decreased bone mass and turn over by inhibiting osteoblast activity. This research suggests that while initial safety profiles with inhibitors such as vorinostat are good, there may be consequences to bones with long term administration of these drugs to people. I contributed to this research through study design, performing most of the experiments and animal work, and writing the paper. Further studies in humans receiving these inhibitors is a goal of future work.

a) McGee-Lawrence M, **McCleary-Wheeler AL**, Secreto F, Radzilo D, Zhang M, Stensgard B, Li X, Lian J, Westendorf J. Suberoylanilide hydroxamic acid (SAHA; vorinostat) causes bone loss by inhibiting immature osteoblasts. *Bone* 2011 May 1;48(5):1117-26. PMC3079070

3. Evaluation of GLI1 downstream of TGF-β1 in the regulation of epithelial to mesenchymal transition. Epithelial to mesenchymal transition (EMT) is an important mechanism to the metastatic potential of solid tumors. Mechanisms regulating EMT are complex and not clearly defined. This work in this study identified the transcription factor GLI1 as functioning downstream of TGFβ. The integral EMT gene, SNAI1, is a direct target of GLI1. This work implicated GLI1 as a mediator of EMT activity in a solid tumor and provided a new link in the regulation of EMT-regulated genes. This data generated from this work suggests that targeting of GLI may inhibit an EMT phenotype in some cancers. I contributed to this work by performing experiments and data analysis. Further evaluations of the GLI transcription factors and their role in modulating an invasive phenotype are ongoing.

a) Zheng X, Vittar NB, Gai X, Fernandez-Barrena MG, Moser CD, Hu C, Almada LL, **McCleary-Wheeler AL,** Elsawa SF, Vrabel AM, Shire AM, Comba A, Thorgeirsson SS, Kim Y, Liu Q, Fernandez-Zapico ME, Roberts LR. The transcription factor GLI1 mediates TGF-β1 driven EMT in hepatocellular carcinoma via a SNAI1-dependent mechanism. *PLoS One*. 2012 7(11):e49581. PMC3501480

Complete List of Published Work in PubMed:
http://www.ncbi.nlm.nih.gov/pubmed/?term=McCleary-Wheeler+A

D. Research Support

Current Research Support:

Private Source McCleary-Wheeler, PI 01/01/17-12/31/19
Private Source
Targeting the Cancer Epigenome: The Effect of Specific Histone Lysine Methyltransferase Inhibition in Canine B-Cell Lymphoma
Understand the role of EZH2 in B-cell lymphomagenesis and the ability to inhibit its activity with a novel, targeted agent.
Role: Principle Investigator

Completed Research Support:

Grant #: N/A Baldanza, Fellow 11/04/15 – 05/31/17
Private Source
The Role of Canonical Hedgehog Signaling in Canine Osteosarcoma
The goal of this project is to determine the activity of hedgehog signaling and evaluate its potential as a novel therapeutic target in canine osteosarcoma.
Role: Mentor

Grant #: N/A Hume, PI 05/01/14–05/31/17
Private Source
A Phase II Investigation of Doxycycline for Canine B-cell Lymphoma
The goal of this project is to determine if doxycycline has single agent efficacy in dogs with previously untreated diffuse large cell B-cell phenotype (DLBCL).
Role: Co-Investigator

Grant #: N/A Peralta, PI 01/01/17-12/31/17
Private Source
Identification of targetable activating mutations in canine acanthomatous ameloblastoma
A pilot study to evaluate the role for BRAF and Smoothened mutations in canine ameloblstomas to determine if specific targeting of these proteins may have clinical therapeutic potential.
Role: Co-Investigator

Private Source McCleary-Wheeler, PI 04/01/16 - 03/31/18
Private Source
A Contemporaneous Controlled Study of the Standard Of Care (SOC) in Dogs with Appendicular Osteosarcoma (COTC022)
The goal of this study is to evaluate the ability of the investigational drug, rapamycin, to prolong progression

free survival over standard of care therapy in dogs with newly diagnosed appendicular osteosarcoma.
Role: Principal Investigator

Private Source McCleary-Wheeler, PI 04/01/16 - 03/31/18
Private Source
Evaluation of Orally Administered MTOR Inhibitor Rapamycin in Dogs in the Adjuvant Setting with Osteosarcoma (COTC021)
The goal of this study is to evaluate the ability of the investigational drug, rapamycin, to prolong progression free survival over standard of care therapy in dogs with newly diagnosed appendicular osteosarcoma.
Role: Principal Investigator

Grant #: N/A McCleary-Wheeler, PI 07/01/16 - 6/30/18
Private Source
The Role of Hedgehog Signaling in Feline Oral Squamous Cell Carcinoma
This project aims to evaluate the role Hedgehog signaling plays in feline oral squamous cell carcinoma and how inhibition of this pathway affects growth and viability of this tumor.
Role: Principal Investigator

1 KL2 TR0002385-01 McCleary-Wheeler, PI 09/05/17-6/30/18
Weill Cornell Clinical and Translational Sciences Center KL2 Scholar Award; National Center for Advancing Translational Sciences
A Comparative Approach to Understanding GLI2 in Diffuse Large B-cell Lymphoma
This project focuses on the study of chromatin regulating enzymes and their role in both canine and human diffuse large B-cell lymphomas.
Role: Principle Investigator, mentored

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Barbara E. Bierer, MD**

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Professor of Medicine and Senior Physician, Brigham and Women's Hospital & Professor of Medicine (Pediatrics), Harvard Medical School

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yale College, New Haven, CT	B.Sc	06/1976	Biology
Harvard Medical School, Boston, MA	M.D.	05/1980	Medicine
Massachusetts General Hospital, Boston MA	Intern/Resident	--	Internal Medicine
Brigham and Women's Hospital, Boston MA	Fellow	--	Hematology Oncology

Personal Statement

I have been committed to the ethical conduct of research, and to optimizing human research protections, for the past three decades. I am the Director of the Regulatory Foundations, Ethics and the Law Program of the Harvard Catalyst, the Harvard Clinical and Translational Science Award, an integrated platform serving over 20 institutions and schools. Through that position, we developed a collaborative model of single IRB review of multisite trials (www.SMARTIRB.org), to which >415 signatories have joined, enabling access to a national collaborative network that we will leverage in this project. I serve as the Director of Regulatory Policy of SMART IRB. Within the Harvard Catalyst, I also worked on developing model reliance agreements for IACUCs (and IBCs). It is this latter work that I trust will be of significant benefit on this current application, and for which I am an enthusiastic collaborator.

In addition, I direct the Multiregional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center, www.MRCTCenter.org), a University-wide and collaborative effort to improve standards for the planning and conduct of clinical trials with a particular focus in emerging economies. In that context, the inclusion of underrepresented populations is critically important, as it is in nationally. My work focuses on the scientific, regulatory, and ethical implications of translational research from pre-clinical to and across the T1-T4 spectrum, for all populations including animals, with particular attention to addressing new and emerging ethical issues, to enabling innovation, and to using administrative flexibility to decrease burden and foster collaboration. It is my personal and professional mission to support translational research across complex enterprises while ensuring that such research rests on a firm foundation of law, ethics, and justice. From 2003-2014, I was Senior Vice President Research at the Brigham and Women's Hospital, responsible for basic, translational, and clinical research, and for compliance with all institutional policies and state and federal regulations related to research. It was this experience that informed my commitment to providing tools for the research community to decrease administrative burden while increasing compliance.

1 Winkler SJ, Witte E, Bierer BE. (2015). The Harvard Catalyst Common Reciprocal IRB Reliance Agreement: an innovative approach to multisite IRB review and oversight. Clin Transl Sci. 8(1): 57-66.

2 Bierer BE, Barnes M. Research misconduct involving noncompliance in human subjects research supported by the public health service: reconciling separate regulatory systems. *Hastings Cent Rep* 2014: Jul-Aug;44(4 Spec No): S2-S26. doi: 10.1002/hast.336

3 Peloquin D, Giampa J, Barnes M, Bierer BE. Certificates of Confidentiality after the 21st Century Cures Act. *Medical Research Law & Policy Report*, 16 MRLR 20, 10/04/2017.

4 Gelinas L, Largent EA, Cohen IG, Kornetsky S, Bierer BE, Lynch HF. A framework for ethical payment to research participants. *N Engl J Med*, 2018:766-771. DOI: 10.1056/NEJMsb1710591.

5 Unpublished

B. Positions and Honors

Positions and Employment:

1980-1983 Intern and Resident in Medicine, Massachusetts General Hospital
1980-1987 Clinical and Research Fellow in Medicine, Harvard Medical School
1984-1987 Research / Clinical Fellow in Medicine, Brigham and Women's Hospital (BWH)
1984-1987 Research Fellow, Pediatric Oncology, Dana-Farber Cancer Institute
1986-1989 Instructor in Medicine, Dana-Farber Cancer Institute and Harvard Medical School
1989-1993 Assistant Professor in Medicine, Dana-Farber Cancer Institute and Harvard Medical School
1994- Active Staff in Pediatric Oncology, Dana-Farber Cancer Institute
1993-1998 Associate Professor in Medicine, Dana-Farber Cancer Institute and Harvard Medical School
1994-1997 Director, Pediatric Bone Marrow and Stem Cell Transplantation, Dana-Farber Cancer Institute and Children's Hospital
1994-1997 Chief, Bone Marrow and Stem Cell Transplantation, Children's Hospital Boston
1995- Associate in Medicine, Children's Hospital Boston
1997-2002 Senior Staff, Clinical Center, National Institutes of Health, Bethesda, MD
1998- Professor of Pediatrics, Harvard Medical School, Dana-Farber Cancer Institute, BWH
1997-2002 Senior Investigator and Attending Physician, Hematology Branch, Clinical Center, NIH
1997-2002 Chief, Laboratory of Lymphocyte Biology, National Heart, Lung, and Blood Institute, NIH
2002- Professor of Medicine (Pediatrics), Harvard Medical School
2002- Active Staff, Dept. of Medicine, Brigham and Women's Hospital and Faulkner Hospital
2002-2003 Vice-President Patient Safety, Director, Center for Patient Safety Dana-Farber Cancer Institute
2003-present Attending Physician, Div. of Hematology, Dept. of Medicine, BWH
2003-2014 Senior Vice President, Research; Brigham and Women's Hospital
2005-2014 Director, Center for Faculty Development and Diversity, Brigham and Women's Hospital
2006-2012 Director, Office for Research Careers, Brigham and Women's Hospital
2007- Director, Regulatory Foundations, Law and Ethics Program, Harvard Catalyst, Harvard Clinical and Translational Science Award, Boston, MA
2009- Faculty Director, Multiregional Clinical Trials Center of BWH and Harvard
2015- Director, Regulatory Policy, SMART IRB, Harvard Medical School and NCATS

Other Experience and Professional Memberships (selected)

1994- 1997 Chief, Bone Marrow and Stem Cell Transplantation, Children's Hospital Boston
1997-1999 Special Assistant to the Scientific Director for Clinical Investigation, NHLBI, NIH
2000- 2007 Board of Directors, Federation of American Societies for Experimental Biology, Bethesda, MD
2001- 2008 Board of Directors, Association for the Accreditation of Human Research Protection Programs, (AAHRPP) Washington, D.C. 2002-2003 Vice-President; 2003-2008 President, AAHRPP
2002-2017 Editor, *Current Protocols in Immunology;* 1990-2008, Associate Editor, Section Editor
2003-2008 National Institutes of Aging, NIH Board of Scientific Counselors
2005-2014 Member, Executive Committee, Brigham and Women's Biomedical Research Institute
2006-2016 Member, Committee on Science, Technology and the Law, The National Academies of Science, Washington DC
2006-2011 Steering Committee, AAMC Forum on Conflicts of Interest Academe
2008-2012 Chair, Secretary's Advisory Committee on Human Research Protections, HHS
2009-2014 Co-chair, Partners Committee on Conflict of Interest, Partners HealthCare, Inc.
2010-2014 Member, HMS Faculty Affairs Advisory Committee
2012-2014 Partners HealthCare Academic Executive Committee
2013- Board of Directors, and Chair, Audit Committee, Management Sciences for Health (MSH), Boston, MA
2013- Board of Directors, Public Responsibility in Medicine and Research, Boston MA
2012-2014 Executive Sponsor, iHub (Innovation Hub), Brigham and Women's Hospital
2012- External Advisory Board, Columbia University Clinical and Translational Sciences Institute
2013- Affiliate Faculty, Petrie Flom Center for Bioethics and the Law, Harvard Law School
2014- Trustee, Edward P. Evans Foundation, New York, NY; 2015- Chair, Board of Trustees

2016- Member, Clinical Research Initiative for Global Health (CRIGH), Paris, France
2014-2016 Member, Committee on Federal Research Regulations and Reporting Requirements: A new Framework for Research Universities in the 21st Century, National Academies of Sciences, Washington DC
2016- Member, Clinical Research Initiative for Global Health (CRIGH), Paris, France
2016- Scientific Advisory Board, Molecular Stethoscope, Inc.
2017- President and Board of Directors, Vivli, Inc
2017- External Advisory Committee, Institute for Advanced Clinical Trials (I-ACT)
2019- Chair, NHLBI IRB for Clinical Data Sciences, NIH, Bethesda MD

Honors (selected)

1988-1992 McDonnell Fellow in Molecular Medicine in Cancer Research, James S. McDonnell Foundation
1992-1997 Established Investigator Award, American Heart Association
1993 American Society for Clinical Investigation
1995-1998 Councilor, American Society for Clinical Investigation
1999 Clinical Center Director's Award, National Institutes of Health, Bethesda, MD
1999 National Heart, Lung, and Blood Institute Director's Award, NIH
2002 Association of American Physicians
2008 Harold Amos Faculty Diversity Award, Harvard Medical School
2015 Health Improvement Institute: Award for Excellence in Human Research Protection Winner
2018 Wallace H. Coulter Distinguished Lecturer, International Society for Laboratory Hematology

C. Contributions to Science

1. I have had a long-standing commitment to data sharing and transparency, including return of aggregate and individual results to participants and sharing of individual patient-level data (IPD). Public understanding of the risks and benefits of sharing IPD is highly variable as is the enthusiasm of investigators and clinicians to share such information. We have recently completed the PCORI-funded Open Science Policy effort to generate template data use agreements, data contributor agreements, and informed consent prototype language all to promote data sharing.

A. Mello MM, Francer JK, Wilenzick M, Teden P, Bierer BE, Barnes M. (2013) Preparing for responsible sharing of clinical trial data. N Engl J Med. 369(17): 1651-8
B. Bierer BE, Li R, Barnes M, Sim I. A Global, Neutral Platform for Sharing Trial Data. N Engl J Med. 2016. 374:2411-3. doi: 10.1056/NEJMp1605348.
C. Bierer BE, Crosas M, Pierce HH. Data Authorship as an Incentive to Data Sharing. *N Engl J Med.* 2017; 376:1684-1687 DOI: 10.1056/NEJMsb1616595.
D. Ohmann C, Banzi R, Canham S, Battaglia S, Matei M, Ariyo C, Becnel L, Bierer B, Bowers S, Clivio L, Dias M, Druml C, Faure H, Fenner M, Galvez J, Shersi D, Gluud C, Groves T, Houston P, Karam G, Kara D, Knowles RL, Krieža-Jerić, Kubiak C, Kuchinke W, Kush R, Lukkarinen A, Marques PS, Newbigging A, O'Callaghan J, Ravaud P, Schlünder I, Shanahan D, Sitter H, Spalding D, Tudur-Smith C, van Reusel P, van Veen E-V, Visser GR, Willson J, Demotes-Mainard J. Sharing and reuse of individual participant data from clinical trials: principles and recommendations. *BMJ Open* 2017;**7:**e018647. doi: 10.1136/bmjopen-2017-018647.
E. Pierce HH, Dev A, Statham E, Bierer BE, Credit data generators for data reuse. 2019 *Nature* 570:30-32. https://nature.com/articles/d41586-019-01715-4

2. Clinically, I have been involved in adult and pediatric stem cell transplantation and more recently, in general hematology. My basic research laboratory interests complemented my clinical responsibilities. Earlier in my career, I explored the mechanism of immunosuppressant action, finding that cyclosporine (CsA) and tacrolimus (FK506) are inert themselves but acquire their activity upon binding to intracellular cognate receptors, cyclophilins (CyPs) and FK506 binding proteins (FKBPs) respectively. The complexes of CsA/CyPs and tacrolimus/FKBPs each bind to and inhibit the serine/threonine phosphatase calcineurin, an enzyme critical for T cell activation. We demonstrated that inhibition of calcineurin activity correlates with inhibition of T cell cytokine and chemokine transcriptional activation, T cell apoptosis, and cytolytic activity; we demonstrated calcineurin inhibition in T lymphocytes derived from CsA-treated allogeneic transplants recipients. Calcineurin targets that we identified may be important in the pathophysiology of the common toxicities (e.g. neurotoxicity and nephrotoxicity) observed clinically with CsA and tacrolimus treatment.

A. Bierer BE, Mattila PS, Standaert RF, Herzenberg LA, Burakoff SJ, Crabtree G, Schreiber SL. 1990. Two distinct signal transduction pathways in T lymphocytes are inhibited by alternative complexes formed between an immunophilin and either FK506 or rapamycin. *Proc Natl Acad Sci USA* 87:9231.

B. Bierer BE, Somers PK, Wandless TJ, Burakoff SJ, Schreiber SL. 1990. Probing immunosuppressant action with a nonnatural immunophilin ligand. *Science* 250(4980):556.
C. Price DJ, Grove JR, Calvo V, Avruch J, Bierer BE. 1992. Rapamycin-induced inhibition of the 70 kilodalton S6 protein kinase. *Science* 257(5072):973
D. Cristillo AD, Nie L, Macri M, Bierer BE. 2003. Cloning and characterization of N4WBP5A, an inducible, CsA-sensitive, Nedd4 binding protein in human T lymphocytes. *J Biol Chem*, 278:34587.

3. A basic understanding of the regulation of T cell activation and of T cell fate is critical for understanding tolerance and auto-immunity. My early research focused on the signal transduction pathways critical for T cell activation and tolerance, with a particular focus on CD28 and CD2. Engagement of CD28 is known to prevent the induction of T cell anergy, while ligation of CD2 has been shown to influence the cytokine profile of activated T cells. We investigated the signaling intermediates recruited by CD28 and by CD2, performed a structure-function analysis of CD2 and characterized its cellular ligands.
   A. Hahn WC, Menu E, Bothwell AJ, Sims P, Bierer BE. 1992 Overlapping but non-identical binding sites on CD2 for CD58 and a second ligand, CD59. *Science* 256(5065):1805.
   B. Hahn WC, Bierer BE. 1993 Separable portions of the CD2 cytoplasmic domain involved in signaling and ligand avidity regulation. *J Exp Med* 178(5):1831.
   C. Hutchcroft JE, Bierer BE. 1994 Activation-dependent phosphorylation of the T lymphocyte surface receptor CD28 and associated proteins. *Proc Natl Acad Sci USA* 91(8):3260.
   D. Martelli MP, Lin H, Zhang W, Samelson LE, Bierer BE. 2000 Signaling via LAT (linker for T cell activation) and Syk/ZAP70 is required for ERK activation and NFAT transcriptional activation following CD2 stimulation. *Blood* 96(6):2181.

4. In 2003, I assumed the role of senior vice president, research at the Brigham and Women's Hospital, a position that was new to the institution and that altered my career path. I closed my basic and translational laboratory and spent considerable effort in research and health policy, with a particular focus on human clinical research. Chairing SACHRP led to many contributions (See SACHRP letters 9-20 at http://www.hhs.gov/ohrp/sachrp/commsec/)that reframed, annotated or suggested changes to human research protections and privacy, and later my role both in the Harvard Catalyst (CTSA) and in the MRCT Center led to policy, guidance and tools to promote the ethical conduct of research. See Section A above, and:
   A. Lynch, HF, Bierer BE, Cohen IG. Confronting biospecimen exceptionalism in proposed revisions to the common rule. Hastings Cent. Rep. 2016 Jan; 46(1):4-5. doi: 10.1002/hast.528.
   B. Bierer BE, Barnes M. Research misconduct involving noncompliance in human subjects research supported by the public health service: reconciling separate regulatory systems. *Hastings Cent Rep* 2014: Jul-Aug;44(4 Spec No): S2-S26. doi: 10.1002/hast.336
   C. Bierer BE, Li R, Seltzer J, Sleeper L, Aldinger C, Frank E, Knirsch C, Levine RJ, Massaro J, Shah A, Barnes M, Snapinn S, Wittes J. Responsibilities of data monitoring committees: Consensus recommendations. Therapeutic Innovation & Regulatory Science. May 13, 2016, doi: 10.1177/2168479016646812.
   D. Nichols L, Brako L, Rivera SM, Tahmassian A, Jones MF, Pierce HH, Bierer BE. What do revised US rules mean for human research? *Science*. 2017; 357: 650-1.
   E. Bierer BE, Strauss DH, White SA, Zarin DA. (2018) Universal funder responsibilities that advance social value. *American J of Bioethics*, 2018:18:11, 30-32. https://doi.org/10.1080/15265161.2018.1523498

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed?term=Bierer+BE&cmd=DetailsSearch
Orcid ID: orcid.org/0000-0001-6448-8170

D. Additional Information: Research Support and/or Scholastic Performance

ACTIVE

1UL1TR002541-01 (Nadler) 05/01/18 – 04/30/23 EFFORT
National Center for Advancing Translational Sciences (Harvard Medical School) $50,434
Harvard Clinical and Translational Science Center
The Harvard Clinical and Translational Science Center is dedicated to improving human health by enabling collaboration and providing tools, training, and technologies to clinical and translational investigators.
Role: Co-I

3UL1TR002541-01S1 (Nadler) 07/15/18 – 04/30/21 EFFORT
National Center for Advancing Translational Sciences (Harvard Medical School) $118,023
The Harvard Clinical and Translational Science Center (SMART IRB)
The overarching goal of this project is to support and enhance the development of a harmonized master reliance agreement, termed SMART IRB, for deployment as a national IRB reliance agreement. To date, over 180 including all the CTSAs have signed the agreement. I serve as the Director of Research Policy and am currently working on harmonization of processes during and after IRB review.
Role: Co-I

No Award Number (Bierer) 12/19/18 – 12/18/20 EFFORT
Private Source $434,752
A New Model for Proactive Safety Surveillance: Collaborating in the Era of Big Data
We propose to convene a variety of stakeholders to discuss whether to consider a new model of proactive safety surveillance, and if so, make progress on defining the characteristics of such a model.
Role: PI

PENDING
Pending Support

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

NAME: London, Cheryl A.

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	COMPLETION DATE	FIELD OF STUDY
Bowdoin College, Brunswick, ME	B.A.	05/1986	Biochemistry
Tufts University, Boston, MA	D.V.M.	05/1990	Veterinary Medicine
University of Wisconsin, Madison, WI	Residency	07/1994	Medical Oncology
Harvard University, Boston, MA	Ph.D.	06/1999	Immunology

A. Personal Statement

I am a veterinary medical oncologist with over 25 years of experience in translational and comparative oncology and drug development. I have been intimately involved in basic and clinical studies involving several anti-cancer therapeutics and have an active laboratory research program interrogating novel targets for therapeutic intervention in sarcoma. As Director of the Clinical Trials Office at the Tufts Cummings School of Veterinary Medicine, I am responsible for overseeing all clinical trials in client owned animals. As Co-Leader of the One Health Program and Director of the Research Collaboration Team at the Tufts Clinical Translational Science Institute, I am charged with expanding and integrating comparative medicine efforts across Tufts and its partners. I have ongoing collaborations with the Broad Institute, Dana Farber Cancer Institute, and Ohio State University as well as several industry partners. During the course of my career, I have been the lead investigator on over 30 translational clinical trials that have necessitated compliance with appropriate institutional and Federal regulatory guidelines, so I am familiar with issues regarding oversight of trials involving client owned animals (pets). Last, I have been intimately involved with recent efforts to expand and optimize the CTSA One Health Alliance through the development of infrastructure and streamlined processes, and am thus well positioned to assist Dr. Moore with the goals outlined in this administrative supplement.

1. Gardner HL, Fenger JM, **London CA**. Dogs as a Model for Cancer. Annu Rev Anim Biosci. 2016; 4:199- 222. PMID: 26566160
2. LeBlanc AK, Breen M, Choyke P, Dewhirst M, Fan TM, Gustafson DL, Helman LJ, Kastan MB, Knapp DW, Levin WJ, **London C**, Mason N, Mazcko C, Olson PN, Page R, Teicher BA, Thamm DH, Trent JM, Vail DM, Khanna C. Perspectives from man's best friend: National Academy of Medicine's Workshop on Comparative Oncology. Sci Transl Med. 2016 Feb 3;8(324):324ps5. PMID: 26843188
3. **London C,** TedxOhioStateUniversity 2015: Of Mice, Dogs, and Men, http://vet.osu.edu/vmc-news/canine-cancer-clinical-trials-discussed-tedxohiostateuniversity-dr-cheryl-london

B. Positions and Honors

Positions and Employment

1995-98 Clinical Instructor, Oncology, Tufts School of Veterinary Medicine, N. Grafton, MA
1996-99 Research Fellow, Immunology Division, Brigham and Women's Hospital, Boston, MA
1999-05 Assistant Professor, UC Davis School of Veterinary Medicine
2005-13 Associate Professor, Veterinary Biosciences, College of Veterinary Medicine, OSU
2007- Director, Veterinary Clinical Research Support Shared Resource, College of Vet Medicine, OSU
2013-16 Shackelford Professor of Veterinary Medicine, College of Veterinary Medicine, OSU
2016- Associated Faculty Professor, College of Veterinary Medicine, OSU
2013-18 Director, Translational Therapeutics Program, Center for Clinical and Translational Sciences, OSU
2014-18 Director, Translational Therapeutics Think Tank, OSU
2016-18 Research Professor, Cummings School of Vet Medicine, Tufts University, Grafton, MA
2016- Director, Clinical Trials Office, Cummings School of Vet Medicine, Tufts University, Grafton, MA
2017- Co-Leader, One Health Program, Cummings School of Vet Medicine and Tufts CTSI, Boston, MA
2018- Director, Research Collaboration Team, Tufts CTSI, Boston, MA
2018- Anne Engen and Dusty Professor of Comparative Oncology, Cummings School, Grafton, MA

2018- Research Professor, Tufts University Medical School, Boston, MA

Honors

1993 Robert S. Brodey Award, for outstanding resident's clinical research
1994 Miles Small Animal Resident of the Year Award
1994 Robert S. Brodey Award, for outstanding resident's basic research
1995-97 John Stauffer Graduate Fellowship
2003 Vintner Grant in Honor of Marc Beringer
2005-16 Shackelford Professor of Veterinary Medicine, OSU
2010 Pfizer Animal Health Research Award
2018 Pfizer Animal Health Research Award

C. Contributions to Science

1. During my residency in veterinary medical oncology, the contribution of KIT signaling to mast cell biology was just being explored. As dogs frequently develop neoplastic diseases of mast cells, I asked whether dog mast cell tumors (MCT) possess mutations in KIT that may contribute to tumor biology. During an externship in the laboratory of Dr. Stephen Galli at Harvard University in 1993, I identified the presence of internal tandem duplications in the juxtamembrane domain of KIT that resulted in ligand-independent KIT signaling. This was the first driver mutation found in canine spontaneous cancer, and my laboratory subsequently defined the role of mutant KIT in canine MCT biology and its utility as a biomarker for mast cell disease.
   a. **London CA**, Kisseberth WC, Galli SJ, Geissler EN, and Helfand SC. Expression of stem cell factor ligand (c-kit) by the malignant mast cells from spontaneous canine mast cell tumors. J Comp Path 115:399-414; 1996. PMID: 9004081
   b. **London CA,** Galli SJ, Yuuki T, Hu Z-Q, Helfand SH, Geissler EN. Spontaneous canine mast cell tumors express tandem duplications in the proto-oncogene c-*kit*. Exp Hematol 27:689-697;1999. PMID: 10210327
   c. Downing S, Chien MB, Kass PH, Moore PF, **London CA**. Prevalence and significance of Kit internal tandem duplications in canine mast cell tumor. Am J Vet Res 63:1718-1723; 2002. PMID: 12492288
   d. Zadovoskaya R, Chien MB, **London CA**. Use of Kit internal tandem duplications to establish mast cell tumor clonality. J Vet Int Med. 18:915-917; 2004. PMID: 15638281

2. The characterization of KIT dysregulation in canine MCT provided an opportunity to evaluate the clinical utility of small molecule inhibitors in the setting of spontaneous disease. To this end, my laboratory worked with Sugen (now Pfizer) during the development and testing of the orally bioavailable multi-targeted kinase inhibitor sunitinib by interrogating the biologic activity of its companion drug toceranib. These studies were critical as earlier inhibitors developed by Sugen had failed both Phase 2 and 3 human clinical trials and there was concern that the newer orally bioavailable compounds would fail to meet clinical endpoints. My laboratory demonstrated inhibition of KIT signaling by toceranib in vitro and defined its safety and efficacy in a Phase 1 study in dogs with spontaneous cancers, providing clear evidence that that sunitinib would likely have biologic activity against KIT-driven malignancies in future human studies. Furthermore, my laboratory performed the first study that demonstrated direct in vivo target modulation (inhibition of KIT phosphorylation) following a single dose of inhibitor in a spontaneous model of disease. Sunitinib was approved for the treatment of imatinib-resistant GIST in 2006 and I led the subsequent pivotal study in dogs with MCT that resulted in the approval of toceranib for dogs with MCT, the first FDA approved cancer therapy in this species.
   a. Liao AT, Chien MB, Shenoy N, Mendel DB, McMahon G, Cherrington JM, **London CA**. Inhibition of constitutively active forms of mutant Kit by a multi-targeted indolinone kinase inhibitor. Blood 15:585-593; 2002. PMID: 12091352
   b. **London CA**,, Hannah A, Zadovoskaya R, Chien MB, Rosenberg ME, Downing S, Post G, Shenoy N, Mendel DB, McMahon G, Cherrington JM. Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies. Clin Cancer Res 9:2755-2768; 2003. PMID:12855656
   c. Pryer NK, Lee LB, Zadovoskaya R, Yu X, Sukbuntherng J, Cherrington JM, **London CA**. Proof of target for SU11654: Kit inhibition in canine mast cell tumors. Clin Cancer Res 9:5729-5734; 2003. PMID: 14654558
   d. **London CA**, Malpais PB, Follis SL, Boucher JF, Rusk A, Rosenberg MP, Henry CJ, Mitchener KL, Klein MK, Hintermeister JG, Bergman PJ, Couto GC, Mauldin GN, Michels GM. Multicenter, placebo-controlled, double-blind, randomized study of oral Palladia (SU11654) in the treatment of dogs with recurrent mast cell tumors. Clin Cancer Res. 15(11):3856-65; 2009. PMID:1947073

3. To better define the biology of malignant mast cell disease, my laboratory developed a technique to generate normal mast cells from canine bone marrow resulting in the generation of a tremendously valuable resource for comparative biology. We demonstrated that canine mast cells possess gene expression profiles and functional properties that are much more comparable to human mast cells when compared to mouse mast cells. Furthermore, the ability to reliably generate canine mast cells enabled us to critically compare the molecular profiles and functional consequences of therapeutic interventions in both normal and malignant mast cell populations. Specifically, we defined the kinetics of HSP90-induced KIT target modulation by ganetespib (STA-9090) prior to human clinical trials and identified KIT as a novel target of the HDAC inhibitor AR42. Lastly, we compared the microRNA profiles of normal and malignant canine mast cells, resulting in the identification of miR-9 as a mediator of invasive behavior and metastasis; a similar role for miR9 has been defined in metastatic human breast cancer. These data supported the development of an inducible mouse model of mast cell specific miR-9 overexpression, supporting the successful K01 application by Dr. Joelle Fenger, for whom I serve as mentor.
    a. Lin T-Z., **London CA**. Functional comparison of canine and murine bone marrow derived cultured mast cells. Vet Imm Immunopathol 114:320-34; 2006. PMID:17027994
    b. Lin TY, Bear M, Du Z, Foley KP, Ying W, Barsoum J, **London CA**. The novel HSP90 inhibitor STA-9090 exhibits activity against Kit dependent and independent malignant mast cell tumors. Exp Hematol. 36:1266-1277; 2008. PMCID: PMC3837096
    c. Lin TY, Fenger J, Muharari S, Bear M, Kulp SK, Wang D, Chen CS, Kisseberth WC, **London CA**. AR- 42, a novel HDAC inhibitor, exhibits biologic activity against malignant mast cell lines via downregulation of constitutively activated Kit. Blood. May 27;115(21):4217-25; 2010. PMCID: PMC3398750
    d. Fenger JM, Bear MD, Volinia S, Lin TY, Harrington BK, **London CA**, Kisseberth WC. Overexpression of miR-9 in mast cells is associated with invasive behavior and spontaneous metastasis. BMC Cancer. Feb 11;14:84. 2014. PMCID: PMC3933481

4. My laboratory has also focused on the comparative biology of canine and human osteosarcoma (OSA) with the ultimate goal of identifying common molecular pathways that provide a foundation for subsequent translational clinical trials. To this end we characterized the contribution of constitutive STAT3 activation to canine OSA, demonstrating that it plays a similar role in disease biology when compared to human OSA. Furthermore, we validated STAT3 as a relevant target for therapeutic intervention in both canine and human OSA. This work resulted in a strong collaborative effort with the OSU College of Pharmacy, OSU College of Medicine, and Nationwide Children's Hospital to develop and test viable allosteric inhibitors capable of specifically targeting STAT3. We demonstrated that the first lead compound, LLL12, exhibits strong in vitro and in vivo biologic activity. A new analog, LY5, was generated that possesses excellent oral bioavailability in both mice and dogs and this compound was extensively evaluated in vitro and in vivo. Importantly, our collaborative work contributed to the successful P01 application, "Studies of Childhood Sarcoma" that integrates in vitro studies, mouse models of disease and spontaneous canine cancer to accelerate and optimize translational efforts.
    a. Fossey SL, Liao AT, McCleese JK, Bear MD, Lin J, Li P, Kisseberth WK, **London CA.** Characterization of STAT3 Activation and Expression in Canine and Human Osteosarcoma. BMC Cancer. Mar 10; 9:81; 2009. PMCID: PMC2666757
    b. Fossey SL, Bear MD, Kisseberth WK, Pennell MJ, **London CA.** Oncostatin M promotes STAT3 activation, VEGF production, and invasion in osteosarcoma cell lines. BMC Cancer. Apr 11;11:125. 2011. PMCID: PMC3079692
    c. Bid HK, Oswald D, Li C, **London C**, Lin J, Houghton PJ. Anti-angiogenic activity of a small molecule STAT3 inhibitor LLL12. PLoS One. 7(4):2012. PMCID: PMC3328460
    d. Yu PY, Gardner HL, Roberts R, Cam H, Hariharan S, Ren L, LeBlanc AK, Xiao H, Lin J, Guttridge DC, Mo X, Bennett CE, Coss CC, Ling Y, Phelps MA, Houghton P, **London CA** Target specificity, in vivo pharmacokinetics, and efficacy of the putative STAT3 inhibitor LY5 in osteosarcoma, Ewing's sarcoma, and rhabdomyosarcoma. PLoS One 12(7):2017. PMCID: PMC5531494

5. A major focus of my scientific efforts has been to evaluate novel therapies in the setting of spontaneous canine disease with the intent of informing the human drug development path. To this end we performed studies in the pre- and post-IND settings that facilitated and informed subsequent human clinical trials. Our work with ganetespib in dogs with spontaneous cancers demonstrated that biologic activity was associated with sustained drug plasma levels between 200-600 ng/ml and established surrogate biomarkers of HSP90

inhibition. A follow-on study to this work defined a dosing regimen for ganetespib that provided both superior downregulation of the HSP90 client protein KIT in canine mast cell tumors which was linked to improved biologic activity. Our clinical trial of the XPO-1 inhibitor verdinexor (KPT-335) in dogs defined the expected adverse event profile and provided strong evidence of biologic activity in lymphoid malignancies, both of which were confirmed in subsequent human clinical trials of the closely related analog selinexor (KPT-335). Lastly, our work with the anti-KIT humanized MAb (KTN0158) in dogs with mast cell tumors was incorporated into the IND application and supported initiation of human clinical trials.

a. **London CA**, Bear MD, McCleese J, Foley KP, Paalangara R, Inoue T, Ying W, Barsoum J. Phase I evaluation of STA-1474, a prodrug of the novel HSP90 inhibitor ganetespib, in dogs with spontaneous cancer. PLoS One. 6(11); 2011. PMCID: PMC3207826
b. **London CA**, Acquaviva J, Smith DL, Sequeira M, Shin Ogawa L, Gardner HL, Feo Bernabe L, Bear MD, Bechtel SA, Proia DA. Consecutive day HSP90 inhibitor administration improves efficacy in murine models of KIT-driven malignancies and canine mast cell tumors. Clin Cancer Res. 2018 Aug 31. pii: clincanres.0703.2018. doi: 10.1158/1078-0432.CCR-18-0703. [Epub ahead of print] PMID:30171047 PMCID: In progress.
c. **London CA**, Bernabe LF, Barnard S, Kisseberth WC, Borgatti A, Henson M, Wilson H, Jensen K, Ito D, Modiano JF, Bear MD, Pennell ML, Saint-Martin JR, McCauley D, Kauffman M, Shacham S. Preclinical evaluation of the novel, orally bioavailable Selective Inhibitor of Nuclear Export (SINE) KPT 335 in spontaneous canine cancer: results of a phase I study. PLoS One. Feb 4;9(2); 2014. PMCID: PMC3913620
d. **London C**, Gardner HL, Rippy S, Post G, LaPerle K, Crew L, Lopresti-Morrow L, Garton AJ, McMahon G, LaVallee TM, Gedrich R. KTN0158, a humanized anti-KIT monoclonal antibody, demonstrates biologic activity against both normal and malignant canine mast cells. KTN0158, a humanized anti-KIT monoclonal antibody, demonstrates biologic activity against both normal and malignant canine mast cells. Clin Cancer Res. 2017 May 15;23(10):2565-2574. PMCID: PMC5418113

My 129 publications are at: https://www.ncbi.nlm.nih.gov/sites/myncbi/cheryl.london.1/bibliography/41676115/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1P01CA165995-01A1 Houghton (PI) 06/01/13-05/31/19
Studies of childhood sarcoma
The purpose of this program project grant is to comprehensively understand the roles of three signaling pathways (NF-kB, STAT3, and insulin like growth factors) in the maintenance of malignant phenotypes of childhood sarcomas, and to develop novel and effective new therapies for treating patients.
Role: PI Core C, Comparative Animal Core; PI Project 2, STAT3 signaling in sarcoma

K01 OD 019923 Fenger (PI) 02/16/15-02/15/20
Dissecting the role of miR-9 in normal and malignant mast cell biology.
This training grant will evaluate the consequences of miR-9 overexpression on normal and malignant mast cell biology using a mouse model that conditionally overexpresses miR-9 in mast cells. *Role: Mentor*

U01CA224153 London/Richards (MPIs) 12/01/17-11/30/22
Enhancing the efficacy of immunotherapy in DLBCL using rational combination approaches.
The purpose of this proposal is to use dogs with spontaneous naïve DLBCL to rapidly evaluate rational small molecule/immunotherapy combination approaches, with the ultimate goal of identifying the most effective combination to move forward in human patients with DLBCL. *Role: PI*

U01 CA224182 Dow/London (MPIs) 12/01/27-11/30/22
Optimizing novel immunotherapy combinations targeting the tumor microenvironment in canine osteosarcoma.
This proposal will test four TME modifying immunotherapy combinations for anti-tumor and immune modulatory activity in dogs with metastatic OS, identifying relevant biomarkers associated with responses to therapy. An adjuvant immunotherapy trial will be completed in dogs with OS with the most active combination. *Role: PI*

1R01 CA218570-01AI Karlsson (PI) 04/01/18-01/30/22
Transforming family dogs into a powerful and accessible model for human cancer
This work will combine the power of cell-free DNA sequencing, enthusiasm of citizen-scientist pet owners, and clinical experience of veterinarians. A research portal for collection of data on diagnosis, treatment, and outcome for thousands of dogs with cancer, as well as their environment and lifestyle will be created. *Role: Co-I*

Private Source London (PI) 03/01/18-11/30/21
Identification of novel synthetic lethal partners to optimize PI3K targeted therapy in canine hemangiosarcoma.
This study will assess expression and function of PI3K isoforms in canine HSA and use combined CRISPR/lenti-sh approaches to generate HSA lines deficient in specific isoforms for identification of synthetic lethal partners. We will also evaluate additional tumor samples for mutations in the PI3K/AKT/mTOR pathway and use this information to design assays that leverage cell-free tumor DNA for monitoring of remission status. *Role: PI*

Private Source London (PI) 03/01/18-02/28/21
Improving outcomes for dogs with hemangiosarcoma.
The purpose of this proposal is to develop and validate a non-invasive blood based method that can be used for early detection of HSA and characterization of the genetic changes over time that drive resistance to therapy, and use this data to identify novel targets for therapy associated with resistance. *Role: PI*

U54 TR002354 Selker (PI) 05/01/18-04/30/23
Tufts Clinical and Translational Science Institute
Through research resources, services, and education, Tufts Clinical and Translational Science Institute supports the entire spectrum of clinical and translational research to help meet the promise and the public's needs of biomedical science. This spectrum includes the translation of bench research into bedside care ("T1"), into effective clinical practice ("T2"), into wide care delivery and public health ("T3"), and into health policy ("T4"). By doing this, we hope to support research that will have impact on healthcare and the public's health.
Role: One Health Optional Module, Director; Collaboration and Multidisciplinary Team Science, Director

UL1TR002544 (Supplement) Selker (PI) 08/01/18-04/30/19
Tufts Clinical and Translational Science Institute
We will build upon ongoing work aimed at connecting COHA and its partners through the veterinary adapted Common Data Model (OMOPV5+) by adding enhanced functionalities to facilitate multi-investigator/multi-institution studies and building a web portal that will serve as a central source of data regarding training/education opportunities, animal model suitability, and community engagement. *Role: Co-Investigator*

Private Source London (PI) 06/01/18-05/30/20
Interrogating the regulation, function and therapeutic potential of monocarboxylate transporters in osteosarcoma.
The purpose of this grant is to investigate how transcriptional dysregulation of MCT expression can be effectively targeted to modulate cellular metabolism in both the tumor cells and tumor microenvironment, resulting in synthetic lethality in combination with standard cytotoxic chemotherapy. *Role: PI*

Private Source London (PI) 08/01/18-07/31/20
Interrogating the therapeutic potential of monocarboxylate transporters in osteosarcoma
The overarching goal of this proposal is to investigate how dysregulated STAT3 activation and altered FOXM1/MCT expression and can be effectively targeted to modulate cellular metabolism, resulting in synthetic lethality in combination with other therapeutics. *Role: PI*

Completed Research Support

3P30CA006516-51 (supplement) Benz (PI) 09/01/16-08/31/18
A Multi-Institutional Approach to Interrogate and Improve Immunotherapy Outcomes in Osteosarcoma This is an Administrative Supplement to the CCSG at the DFCI/Harvard to support genomic analysis of the canine osteosarcoma tumor genome as a prelude to future immunotherapy clinical trials in dogs with osteosarcoma. This is a joint effort between the DFCI, Broad Institute, and Tufts University. Role: Consortium Project Director

UL1TR001070 (Supplement) Jackson (PI) 09/15/16-04/30/18
Optimizing Translational Veterinary Trials to Advance Human Outcome
This is an Administrative Supplement to the CSTA award at the OSU to optimize a set of standard operating practices and procedures for veterinary trials initially developed at OSU and implement these across a network of the 15 veterinary academic centers in the CTSA One Health Alliance (COHA) ultimately creating a highly trained and functional veterinary clinical trials consortium. Role: Project Leader

Private Source London (PI) 09/01/13-02/01/17
Role of miR-9 overexpression in canine osteosarcoma
The studies outlined in this proposal will provide a molecular framework for understanding the process of miR-9 driven metastasis in canine OSA. Role: PI

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: David Evan Lee-Parritz

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Clinical Professor and Chair, Department of Environmental and Population Health

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yale College, New Haven CT	BA	05/1979	History
Tufts University School of Veterinary Medicine, North Grafton MA	DVM	05/1983	Veterinary Medicine
Tufts University School of Veterinary Medicine, North Grafton, MA	Resident	05/1987	Small Animal Internal Medicine
American College of Laboratory Animal Medicine	Diplomate	07/1995	Laboratory Animal Medicine

A. Personal Statement

I am a laboratory animal veterinarian with 30 years' experience with research animal care and use with a record of leadership and management. I have a track record of independent and collaborative studies using a wide range of laboratory animal species. I am recognized for my ability to develop consensus-driven solutions to difficult problems with multiple stakeholders. I am widely recognized as an expert in the preventive medicine and clinical care of rodents, nonhuman primates, livestock and many less-common research species. One of my most enjoyable challenges as a laboratory animal veterinarian is to collaborate with faculty and staff on innovative solutions to complex scientific and logistical challenges. I offer a diverse background in academic and pharmaceutical biomedical research.

B. Positions and Honors

Positions

1983 - 1984 Associate Veterinarian, McGrath Animal Hospital, Billerica MA
1984 - 1987 Resident, Small Animal Internal Medicine, Tufts University School of Veterinary Medicine
1987 - 1997 Chief, Unit of Primate Medicine, New England Regional Primate Research Center, Harvard Medical School
1997 – 2003 Associate Director for Operations, Center for Animal Resources and Comparative Medicine Harvard Medical School
2003 – 2006 Animal Research Director, Department of Comparative Medicine, Genzyme Corporation
2006 – 2013 Animal Research Senior Director, Department of Comparative Medicine, Genzyme Corporation

2013 – present Clinical Professor and Director, Laboratory Animal Medicine Service, Department of Environmental and Population Health, Cummings School of Veterinary Medicine. Professor, Tufts Clinical and Translational Sciences Institute
2015 – present Chair, Department of Environmental and Population Health, Cummings School of Veterinary Medicine

Licensure and Certification
Board Certification - American College of Laboratory Animal Medicine 1995
Licensure – Massachusetts (Veterinary Medicine)

Honors (selected)
2007 Henry E. Childers Award, Tufts University Cummings School of Veterinary Medicine
1987 Best Presentation Award, American Animal Hospital Association Resident's Day

C. Contributions to Science

As a laboratory animal veterinarian, I have an important role in the diagnosis and management of laboratory animal disease, and in the development and application of animal models for the solution of urgent human and animal health problems. In collaboration with scientists, I apply the "3R's" to use the appropriate number of animals and to refine the experimental design to prevent or minimize animal pain and distress.

1. Chen ZW, Zhou DJ, Chalifoux L, Lee-Parritz D, Mansfield K, Lord CI, Letvin NL. Disseminated granulomatous disease in a simian immunodeficiency virus and Bacille-Calmette-Guerin-infected rhesus monkey (Letter). AIDS 1997; 11:266-267.
2. Moghaddam A, Rosenzweig M, Lee-Parritz D, Annis B, Johnson RP, Wang F. An animal model for acute and persistent Epstein-Barr virus infection. Science 1997; 276: 2030-2033.
3. Lee-Parritz, D., Cowell, A., Serriello, R., & Erickson, G. (2011). Response to Protocol Review Scenario: within his rights. Lab animal, 40(4), 104-104.
4. Lee-Parritz, D., Holm, A., & Flink, K. (2015). Safety is the main concern. Lab Animal, 44(8), 296. doi:10.1038/laban.824

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/52007664/

D. Additional Information: Research Support and/or Scholastic Performance

Completed Research Support (last three years)

Private Source PI: David Lee-Parritz 8/2013 – 7/2017
Title: Sponsorship of Animal Welfare Speakers at Cummings School.
Goal: Travel expenses and honoraria for outside speakers to address animal welfare related topics of interest to DVM and MAPP students.

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Helen O'Meara

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Associate Director, IACUC/IBC

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bowling Green State University, Bowling Green OH	BS	06/1984	Biology and Environmental Science
Case Western Reserve University, Cleveland OH	MS	12/1993	Environmental Health Science

A. Personal Statement

I have over 13 years of experience providing leadership for the administrative, regulatory and programmatic activities supporting The Ohio State University's animal research program. Prior to this role, I had over 10 years leading animal toxicology studies and preparing assessments required by regulatory agencies for the registration of new products. I have presented IACUC regulatory requirements in presentations both locally and at national conferences for IACUC administrators. I have also worked in close collaboration with other IACUC administrators as part of the Big Ten Academic Alliance IACUC Administrators subgroup in sharing best practices. I am interested in improving efficiencies for regulatory reviews and reducing regulatory burdens.

B. Positions and Honors

01/1990 – 09/2001	Study Director, Team Leader, Ricerca LLC, Painesville Ohio
10/2001 – 11/2002	Executive Director, Ohio League of Conservation Voters, Columbus Ohio
02/2006- 05/2007	IACUC Quality Improvement Specialist, The Ohio State University
05/2007- present	Associate Director, IACUC/IBC, The Ohio State University

12/2018	Lean Six Sigma Greenbelt Certification
2006- present	Member, PRIM&R, Public Responsibility in Medicine and Research
2017- present	Member, National planning committee for PRIM&R IACUC meeting
04/2008- present	Certified Professional in IACUC Administration
1986-1991	Member, Association for Laboratory Animal Science, certified as Laboratory Animal Technologist
1984	Phi Beta Kappa

C. Contributions to Science

2010 National PRIM&R meeting – presentation “Formal and Informal Approaches to Post-Approval monitoring: What works and Why?”

2017 National PRIM&R meeting – presentation “Using Data to Evaluate and Improve your Animal Care and Use Program”

2018 National PRIM&R meeting – presentation “Keeping the Key Players in your Animal Care and Use Program Informed and Engaged”

2019 National PRIM&R meeting – presentation “Regulatory Nirvana: An Engaged Research Team Committed to Compliance and Beyond”

D. Additional Information: Research Support and/or Scholastic Performance

Program Director/Principal Investigator (Last, First, Middle):

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Jeffrey R Henegar	Director, Animal Care and Quality Assurance Director, Office of Animal Resources
eRA COMMONS USER NAME (credential, e.g., agency login) eRA Commons User Name	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Missouri, Columbia, MO	B.A.	1987	Biological Sciences
University of Missouri, Columbia, MO	M.A.	1990	Biological Sciences
University of Missouri, Columbia, MO	Ph.D.	1996	Physiology
Univ. of Mississippi Medical Center, Jackson, MS	Postdoc	1999	Physiology & Biophysics

A. Personal Statement.

I am the Director of Animal Care Quality Assurance and the Office of Animal Resources at The University of Missouri. The University of Missouri is committed to the humane care and use of animals in research and teaching, and to adhere to applicable laws, principles, standards, guidelines and policies affecting such use. Our researchers and scientists share that commitment and are diligent in their work to protect human and animal welfare. In my role, I am directly involved in the oversight and approval of animal use protocols at our institution, including those that involve the use of client-owned animals (veterinary clinical trials). I work closely with faculty in the College of Veterinary Medicine who are involved in translational research projects using natural animal models of disease. I am excited to serve as a co-investigator on this proposal to work toward a streamlined and efficient process for review and approval of veterinary clinical trials both at University of Missouri and across the COHA network.

B. Positions and Honors

Positions

2019-Present Director, Office of Animal Resources
2013-Present Director, Animal Care Quality Assurance, University of Missouri, Columbia, MO
2013-Present Comparative Medicine Faculty, University of Missouri, Columbia, MO
2014-Present Associate Professor of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO
2005-2013 Associate Professor of Pathology, University of Mississippi Medical Center, Jackson, MS
2005-2013 Assistant Professor of Physiology & Biophysics, Univ. of Mississippi Med. Center, Jackson, MS
1999-2005 Assistant Professor of Pathology, University of Mississippi Medical Center, Jackson, MS
1999-2013 Director of Electron Microscopy, Department of Pathology, University of Mississippi Medical Center, Jackson, MS
1999-2013 Faculty Member, Center for Cardiovascular-Renal Research, University of Mississippi Medical Center, Jackson, MS
1998-1999 Instructor of Physiology, University of Mississippi Medical Center, Jackson, MS
1996-1998 Research Associate, University of Mississippi Medical Center, Jackson, MS
1993-1996 Senior Research Specialist, University of Missouri, Columbia, MO
1990-1993 Research Specialist, University of Missouri, Columbia, MO

Honors

Graduate School: Outstanding Graduate Teaching Assistant Award (twice), Losartan Travel Award Recipient

Professional: Merck Young Investigators Award- AHA Council for High Blood Pressure Research, Caroline tum Suden/Frances A. Hellebrandt Professional Opportunity Award- American Physiological Society

C. Contributions to Science

1. Henegar JR, Maruniak JA. Quantification of the effects of unilateral naris closure on the olfactory bulbs of adult mice. Brain Res. 568: 230-234, 1991.
2. Corotto FS, Henegar JR, Maruniak JA. Neurogenesis persists in the subependymal layer of the mouse brain. Neuroscience Letters 149: 111-114, 1993.
3. Corotto FS, Henegar JR, Maruniak JA. Odor deprivation leads to reduced neurogenesis and reduced neuronal survival in the olfactory bulb of the adult mouse. Neuroscience. Aug;61(4):739 44, 1994.
4. Kabour A, Henegar JR, Janicki JS. Angiotensin II (AII)-induced myocyte necrosis: Role of the AT1 receptor. J. Cardiovasc. Pharmacol. 23: 547-553, 1994.
5. Janicki JS, Henegar JR, Campbell SE, Tyagi SC. Myocardial collagenase in experimental cardiomyopathy. In Wound Healing in Cardiovascular Disease Weber KT (ed), Futura Publishing Co., Boston, pp. 73-81, 1994.
6. Kabour A, Henegar JR, Devineni VR, Janicki JS. Prevention of angiotensin II induced myocyte necrosis and coronary vascular damage by lisinopril and losartan in rats. Cardiovasc Res 29:543-548, 1995.
7. Janicki JS, Tyagi SC, Campbell SE, Reddy HK, Henegar JR. Progressive ventricular dilatation in heart failure: the role of myocardial collagenase. In Heart Hypertrophy and Failure Dhalla NS, Pierce GN, Panagia V, Beamish RE (eds), Kluwer Academic Publishers, Boston, pp. 261-273, 1995.
8. Henegar JR, Brower G, Kabour A, Janicki JS. Catecholamine response to chronic angiotensin II infusion and its role in myocyte and coronary vascular damage. Am J Physiol 269:H1564-H1569, 1995.
9. Janicki JS, Brower GL, Henegar JR, Wang L. Ventricular remodeling in heart failure: the role of myocardial collagen. Adv. Exp. Med. Biol. 382: 239-45, 1995.
10. Janicki JS, Brower GL, Henegar JR. Interstitial collagen in chronic heart failure. BAM 5(4): 339-348, 1995.
11. Brower GL, Henegar JR, Janicki JS. Temporal evaluation of left ventricular remodeling and function in rats with chronic volume overload. Am. J. Physiol. 271:H2071-H2078, 1996.
12. Janicki JS, Campbell SE, Henegar JR, Brower GL. Myocardial interstitial collagen matrix remodeling in response to a chronic elevation in ventricular preload or afterload. In Cardiac-Vascular Remodeling and Functional Interaction. Maruyama Y, Hori M, Janicki JS. (eds.) Springer-Verlag, Tokyo, 19-31, 1997.
13. Henegar JR, Schwartz DS, Janicki JS. AngII-related myocardial damage: role of cardiac sympathetic catecholamines and □-receptor regulation. Am. J. Physiol. 275:H534-H541, 1998.
14. Hall JE, Brands MW, Henegar JR, Shek EW. Abnormal kidney function as a cause and a consequence of obesity hypertension. Clin. Exp. Pharmacol. Physiol. 25(1):58-64, 1998.
15. Hall JE, Brands MW, Shek EW, Henegar JR. Renal actions of angiotensin II and long-term blood pressure regulation. In Renin-Angiotensin, Ed. H. Ulfendahl and M. Aurell, Portland Press Ltd, London, pp. 89-104, 1998.
16. Hall JE, Brands MW, Shek EW, Henegar JR. The renin-angiotensin system and control of renal function. In One Hundred Years of the Renin-Angiotensin System: Past Accomplishments and Future Prospects. Ed. MG Nichols, Portland Press, London, pp. 89-104, 1998.
17. Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. J. Am. Soc. Nephrol. 10:S258-65, 1999.
18. Hall JE, Brands MW, Jones DW, Shek EW, Henegar JR. Mechanisms of obesity hypertension and relevance to essential hypertension. In Obesity: Impact on Cardiovascular Disease. Eds. Fletcher G, Grundy S, Hayman L. Futura Publishing, Inc, 133-153, 1999.
19. Henegar JR, Brower GL, Janicki JS. Characteristics and mechanisms of angiotensin II-related myocardial damage. In Angiotensin II Receptor Blockade: Physiological and Clinical Implications. Dhalla NS, Zahradka P, Dixon IMC, Beamish RE (eds.) Kluwer Academic Publications, 1999.
20. Hall JE, Brands MW, Henegar JR. Mechanisms of hypertension and kidney disease in obesity. Annals New York Acad. Sci. 892:91-107, 1999.
21. Hall JE, Brands MW, Shek EW, Henegar JR. Obesity, Insulin Resistance, and the Renal Circulation. In The Renal Circulation. Anderson, WP, Evans RG, Stevenson,KM (eds), Jai Press Inc., Stamford, Connecticut, pp. 383-397, 2000.

22. Fitzgerald SM, Henegar JR, Brands MW, Henegar LK, Hall JE. Cardiovascular and renal responses to a high fat diet in Osborne Mendel rats. Am J Physiol RegulIntegrComp Physiol. 281(2):R547 52, 2001.
23. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 12(6):1211 7, 2001.
24. Hughson MD, He Z, Henegar J, McMurray R. Alveolar hemorrhage and renal microangiopathy in systemic lupus erythematosus. Arch Pathol Lab Med. 125(4):475 83, 2001.Bahrami D, Henegar JR, Baliga R. Fibrillary glomerulopathy in a 10-year old female. Pediatr. Nephrol. 16(11): 916-8, 2001.
25. Cox MJ, Sood HS, Hunt MJ, Chandler D, Henegar JR, Aru GM, Tyagi SC. Apoptosis in the left ventricle of chronic volume overload causes endocardial endothelial dysfunction in rats. Am J Physiol Heart Circ Physiol. 2002 Apr;282(4):H1197 205.
26. Liu H, Bigler SA, Henegar JR, and Baliga R: Cytochrome P450 2B1 mediates oxidant injury in puromycin induced nephrotic syndrome. Kidney International 2002 Sep;62(3):868-76.
27. Henegar J, Coleman J, Cespedes J, Hughson M. Glomerular calicification may exceed tubulointerstitial calcification in hypercalcemic nephropathy. Arch Pathol Lab Med. 2003 Feb;127(2):E80-5.
28. Flessner M, Henegar J, Bigler S, Genous L. Is the peritoneum a significant transport barrier in peritoneal dialysis? Perit Dial Int. 2003; 23(6): 542-9.
29. Hall JE, Henegar JR, Dwyer TM, Liu J, Da Silva AA, Kuo JJ, Tallam L. Is obesity a major cause of chronic kidney disease? Adv Ren Replace Ther. 2004; 11(1): 41-54.
30. Vera T, Henegar JR, Drummond HA, Rimoldi JM, Stec DE. Protective effect of carbon monoxide-releasing compounds in ischemia-induced acute renal failure. J Am Soc Nephrol. 2005;16(4):950-8.
31. Flessner MF, Choi J, Vanpelt H, He Z, Credit K, Henegar J, Hughson M. Correlating structure with solute and water transport in a chronic model of peritoneal inflammation. Am J Physiol Renal Physiol. 2006 Jan;290(1):F232-40.
32. Vig PJ, Lopez ME, Wei J, D'Souza DR, Subramony S, Henegar J, Fratkin JD. Glial S100B Positive Vacuoles In Purkinje Cells: Earliest Morphological Abnormality In SCA1 Transgenic Mice. J Neurol Sci Turish. 2006;23(3):166-174.
33. Flessner MF, Credit K, Henderson K, Vanpelt HM, Potter R, He Z, Henegar J, Robert B. Peritoneal changes after exposure to sterile solutions by catheter. Am Soc Nephrol. 2007 Aug;18(8):2294-302.
34. Flessner MF, Credit K, Richardson K, Potter R, Li X, He Z, Hoskins G, Henegar J. Peritoneal inflammation after twenty-week exposure to dialysis solution: effect of solution versus catheter-foreign body reaction. Perit Dial Int. 2010 May;30(3):284-93. Epub 2010 Feb 11.
35. Whitley DS, Yu K, Sample RC, Sinning A, Henegar J, Norcross E, Chinchar VG.Virology. 2010 Sep 30;405(2):448-56. Epub 2010 Jul 14.Frog virus 3 ORF 53R, a putative myristoylated membrane protein, is essential for virus replication in vitro.
36. Zhou X, Mao J, Ai J, Deng Y, Roth MR, Pound C, Henegar J, Welti R, Bigler SA. Identification of plasma lipid biomarkers for prostate cancer by lipidomics and bioinformatics. PLoS One. 2012;7(11):e48889. doi: 10.1371/journal.pone.0048889. Epub 2012 Nov 12.
37. Lohmeier TE, Iliescu R, Liu B, Henegar JR, Maric-Bilkan C, Irwin ED. Systemic and renal-specific sympathoinhibition in obesity hypertension. Hypertension. 2012 Feb;59(2):331-8. Epub 2011 Dec 19.
38. Espana EM, Huang B, Fratkin J, Henegar J. An enzymatic technique to facilitate air separation of the stroma-Descemet's membrane junction. Invest Ophthalmol Vis Sci. 2011 Dec 9;52(13):9327-32.
39. Henegar JR, Zhang Y, Rama RD, Hata, C, Hall ME, Hall JE Catheter-based radiofrequency renal denervation lowers blood pressure in obese hypertensive dogs. Am. J. Hypertension 2014 27(10):1285-92.
40. Westbrook L, Johnson AC, Regner KR, Wiliams JM, Mattson DL, Kyle PB, Henegar JR, Garrett MR. Genetic susceptibility and loss of Nr4a1 enhances macrophage-mediated renal injury in CKD. J. Am. Soc. Nephrol. 2014 Apr 10 (Epub ahead of print).
41. White WB, Galis ZS, Henegar J, Kandzari DE, Victor R, Sica D, Townsend RR, Turner JR, Virmani R, Mauri, L. Renal denervation therapy for hypertension: pathways for moving development forward. J. Am. Soc. Hypertens. 2015 May; 9(5): 341-50.
42. Henegar JR, Zhang Y, Hata C, Narciso I, Hall ME, Hall JE. Catheter-based radiofrequency renal denervation: Location effects on renal norepinephrine. Am J Hypertens 2015: 28(7):909-14.
43. Zhou X, Mao J, Ai J, Youping D, Roth MR, Pound C, Henegar J, Welti R, Bigler SA. Identification of plasma lipid biomarkers for prostate cancer by lipidomics and bioinformatics. Plos One 7(11), e48889 Nov 2012.

44. Henegar, JR, Zhang Y, DeRama R, Hata C, Hall ME, Hall JE. Catheter-based radiofrequency renal denervation lowers blood pressure in obese hypertensive dogs. Am. J. Hypertens. 2014: 27(10): 1285-92.
45. Westbrook L, Johnson AC, Regner KR, Williams JM, Mattson DL, Kyle PB, Henegar JR, Garrett MR. Genetic susceptibility and loss of NR4a1 enhances macrophage-mediated renal injury in CKD. 2014: J. Am. Soc. Nephrol. 25(11): 2499-510.
46. White WB, Galis ZS, Henegar J, Kandzari DE, Victor D, Sica D, Townsend RR, Turner JR, Virmani R, Mauri L. J. Am. Soc. Hypertens. 2015 May; 9(5): 341-50. PMID: 25979410.
47. Henegar JR, Zhang Y, Hata C, Narciso I, Hall ME, Hall JE. Catheter-based radiofrequency renal denervation: Location effects on renal norepinephrine. Am. J. Hypertens. 2015: Am. J. Hypertens. 2015 Jul; 28(7): 909-14. PMID 25576624.
48. Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden. FASEB, AAMC, and COGR Workshop, October 2017.

D. Additional Information: Research Support and/or Scholastic Performance
None

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Valerie Joy Parkison

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Regulatory Director

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Michigan State University, East Lansing, MI	BS	05/1998	Zoology
Tufts University School of Veterinary Medicine, North Grafton MA	MS	11/2002	Animals and Public Policy

A. Personal Statement

I am the regulatory compliance director at Tufts University and Tufts Medical Center. I have 19 years of experience working in the regulatory environment for the use of animals in research, teaching, and training. I have a track record of creating efficiencies to ensure compliance while also serving to minimize administrative burden. Therefore, I have taken on increasing responsibilities in other areas of research oversight; such as, biohazardous, chemical, select agents, laboratory safety, clinical research (human and animal) and wildlife/international projects. In recent years, I have also created multi-institutional procedures to fill in the regulatory gap for privately-owned animals used in research and teaching. An important focus for me is to devise solutions that are translatable across multiple and often discrepant areas of oversight, so that compliance is more easily achieved. For this proposal, I offer a broad range of experience with research regulations and institutional solutions.

B. Positions and Honors

Positions

2002 - 2007 IACUC Administrator, Office of the Vice Provost, Tufts University
2007 – 2014 IACUC/IBC Manager, Office of the Vice Provost, Tufts University
2014 – present Regulatory Director, Office of the Vice Provost for Research, Tufts University

Licensure and Certification

Certified Professional IACUC Administrator

C. Contributions to Science

Parkison, V. (2006). Making sense of multiple protocols and grant applications. Failure of compliance by confusion? Lab Animal, 35, 15-16. DOI:10.1038/laban0906-15b

Parkison, V. (2004). Virtual IACUC Meetings: Compliant or Not? Flexibility and focus. Lab Animal,33(4),15-7 DOI:10.1038/laban0404-15a

Roberts, S. Parkison, V. Blaisdell, A.P., Cook. R.G. (2001). Object-based video discriminations in pigeons. Paper presented at the annual meeting of the Conference on Comparative Cognition. Melbourne, FL.

Cook. R.G., Levison, D. Parkison, V. & Blaisdell, A. (2001). Long-term associative memory in pigeons. Paper presented at the annual meeting of the Psychonomic Society, Orlando, FL.

Young, E.A., Altemus, M. Parkison, V. Shastry, S. (2001). The Effects of Estrogen Antagonists and Agonists on the ACTH Response to Restraint Stress in Female Rats. Neuropsychopharmacology, 25, 881-891 DOI: 10.1016/S0893-133X(01)00301-3

D. Additional Information: Research Support and/or Scholastic Performance

N/A

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Valerie K. Bergdall	Director, University Laboratory Animal Resources Professor, Clinical Veterinary Preventive Medicine
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Purdue University, West Lafayette IN	BS	05/81	Biology, Chemistry minor with Secondary Education Certification
Purdue University, West Lafayette IN	DVM	05/88	Veterinary Medicine
University of Michigan, Ann Arbor MI	Residency	06/94	Laboratory Animal Medicine

A. Personal Statement

I am the Director of the University Laboratory Animal Resources and the Institutional Attending Veterinarian at The Ohio State University. I am aware of the critical need to harmonize veterinary clinical trial review processes across veterinary medical institutions in order to promote robust, collaborative, and efficient translational science while promoting best practices in research using client-owned animals.

My background is well-suited to serve as a collaborator on this project. As a board-certified laboratory animal veterinarian, and the Attending Veterinarian for The Ohio State University, I work daily with investigators studying disease in both purpose-bred and client-owned animals. I am well-versed in the regulatory requirements associated with animal research. I have also recently worked Dr. Moore and her colleagues at the OSU Veterinary Medical Center to develop a local process for veterinary clinical trial review with addresses the complex mixture of ethical and regulatory requirements inherent to the use of clinical disease models in animals.

I look forward to the development of a SMART IACUC process which will decrease regulatory burden for multi-center veterinary clinical trials while improving reproducibility and rigor of translational data obtained from these studies.

B. Positions and Honors

Positions and Employment

9/81 to 9/84	Research Associate, Animal Care Sup., Indiana Univ. School of Med., Ft. Wayne, IN
9/84 to 12/87	Research Associate (part-time), Indiana University School of Medicine, Ft. Wayne, IN
6/88 to 6/91	Associate Veterinarian, Pine Valley Veterinary Clinic, Ft. Wayne, IN
6/88 to 6/91	Consulting Lab. Animal Vet., Indiana Univ.-Purdue Univ. at Ft. Wayne, Ft. Wayne, IN
7/91 to 6/94	Postdoctoral Resident, Laboratory Animal Medicine, Univ of Michigan, Ann Arbor, MI
7/94 to 6/98	Assistant Director, Univ. Lab. Animal Resources, The Ohio State Univ., Columbus, OH
7/94 to 7/03	Assistant Professor, Clinical, College of Vet. Prev. Med., The Ohio State Univ., Columbus, OH
7/98 to 5/06	Associate Director, Univ. Lab. Animal Resources, The Ohio State Univ., Columbus, OH
7/03 to 10/07	Associate Professor, Clinical, College of Vet. Prev. Med., The Ohio State University, Columbus, OH

10/04 to 7/09	ACLAM Program Director, Lab. Animal Med. Training Program, The Ohio State University, Columbus, OH
6/06-12/06	Deputy Director, Univ. Lab. Animal Resources, The Ohio State Univ., Columbus, OH
12/06-12/07	Interim Director, Univ. Lab. Animal Resources, The Ohio State Univ., Columbus, OH
10/07-present	Professor, Clinical, College of Vet. Prev. Med., The Ohio State Univ., Columbus, OH
1/08-Present	Director, Univ. Lab. Animal Resources, The Ohio State University, Columbus, OH

Other Experience and Professional Memberships

Licensures:
- Indiana and Ohio Veterinary Medical license
- Indiana Academy of Veterinary Medicine certification

American College of Laboratory Animal Medicine
- Training Program Oversight Committee member, 2006-2009
- Training Program Oversight Committee chair 2008
- 2008 Minimal Competency Panel member
- 2008 Standard Setting Study member
- Certification Oversight Committee member 2009-present
- Mentoring Committee member 2008-2012

American Veterinary Medical Association
American Association for Laboratory Animal Science
Phi Zeta Honor Society
Ohio Scientific Education & Research Association Treasurer, 2001-2006
American Society of Laboratory Animal Practitioners
- Student Liaison for OSU 2001-2008
- Veterinary Student Liaison Committee 2006-2009

Center for Minimally Invasive Surgery member, The Ohio State University
Davis Heart and Lung Research Institute member 2003-present
NCRR Scientific Reviewer 2007-present
- Chair, Special Emphasis Scientific Review Group; 2012, 2013

Center for Critical Care member 2008-present

Honors

1987	Phi Zeta Research Award
1988	Phi Zeta Honor Society
1988	Hill Award for Proficiency in Sm. Animal Nutrition
1995	ACLAM board certification

C. Contribution to Science

1) As evidenced by the publications noted below, my primary contribution to science has been in the field of wound healing and the development of relevant animal models to mimic and further investigate human health concerns. My extensive experience as a veterinarian practicing in a research setting, has allowed me to fully understand the human clinical concern that is driving the research investigation, and help to identify and further develop the appropriate animal model. I have worked with the wound healing group for over ten years and during that period we have developed animal models to address a variety of wound healing concerns such as ischemia, burn, biofilm, diabetes, and metabolic syndrome to further elucidate our understanding of the impact of these conditions on the wound healing process.

1. Gnyawali SC, Barki KG, Mathew-Steiner SS, Dixith S, Vanzant D, Kim J, Dickerson JL, Datta S, Powell H, Roy S, Bergdall V, Sen CK. High-resolution harmonics ultrasound imaging for non-invasive characterization of wound healing in a pre-clinical swine model.PLoS One. 2015 Mar 23;10(3):e0122327.
2. Mixed-species biofilm compromises wound healing by disrupting epidermal barrier function. Roy S, Elgharably H, Sinha M, Ganesh K, Chaney S, Mann E, Miller C, Khanna S, Bergdall VK, Powell HM, Cook CH, Gordillo GM, Wozniak DJ, Sen CK. J Pathol. 2014 Aug;233(4):331-43.

3. Roy S, Driggs J, Elgharably H, Biswas S, Findley M, Khanna S, Gnyawali U, Bergdall VK, Sen CK. Platelet-rich fibrin matrix improves wound angiogenesis via inducing endothelial cell proliferation. Wound Repair Regen. 2011 Nov;19(6):753-66.

2) Another area of research interest relates to refinement of animal care in support of biomedical research. This refinement applies to the animal care itself and/or to the regulatory process involved in using animals.

1. Lewis, S. D., Hickman-Davis, J., & Bergdall, V. K. (2016). Institutional animal care and use committee considerations regarding the use of virus-induced carcinogenesis and oncolytic viral models. *ILAR Journal / National Research Council, Institute of Laboratory Animal Resources, 57*(1), 86-94.
2. Nicolaus, M. L., Bergdall, V. K., Davis, I. C., & Hickman-Davis, J. (2016). Effect of ventilated caging on water intake and loss in 4 strains of laboratory mice. *Journal of the American Association for Laboratory Animal Science: JAALAS, 55*(5), 525-533.
3. The cost of self-imposed regulatory burden in animal research. Thulin JD, Bradfield JF, Bergdall VK, Conour LA, Grady AW, Hickman DL, Norton JN, Wallace JM. FASEB J. 2014 May 1.
4. Effectiveness of shoe covers for bioexclusion within an animal facility. Hickman-Davis JM, Nicolaus ML, Petty JM, Harrison DM, Bergdall VK. J Am Assoc Lab Anim Sci. 2012 Mar;51(2):181-8.

Complete list of published works: http://www.ncbi.nlm.nih.gov/pubmed/?term=bergdall+V

D. Research Support

Ongoing Research Support

2016 Co-Investigator. Roy, Sashwati. "Development of a porcine maxilla-facial thermal trauma model ," Department of Defense, $308K.

2016 Co-Investigator. R01NR015676 Sen, Chandan K. "Wound healing endpoint and recurrence,"

Completed Research Support

1996 NIH Facility Renovation Grant "Renovation of Wiseman Hall Lab. Animal Facility" 1 G20 RR11717-01A1 ($940,418.00)

1998 Private Source "Development of a Noninvasive Pharmacokinetic Model of Biliary drug Metabolism" ($11,926.60)

1999 C06 RR14560-01 "Vivarium expansion to support new initiatives in cardiopulmonary research," NIH/NCRR, $1,771,420.

1999 Private Source "Efficacy of dental implant procedures utilizing a dog model" ($12,000.00)

2002 G20 RR16222-01A1 "Graves Hall Vivarium Renovation," NIH/NCRR, $1,300,000.

2002 "Effects of housing conditions on operant-conditioned rats" Bergdall, VK, M Sarter, and C Kraly. Private Source ($19,482.00)

2007 Co-Investigator. R01 GM077185 "Tissue oxygenation and wound angiogenesis," NIGMS $264,000.

2011 Co-Investigator. Alginate Oligomers to Treat Infectious Microbial Biofilms," Log No. 10099005, Department of Defense

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BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Jessica L Evans

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Program Manager, IRB Agreements & Regulatory Support

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Miami University, Oxford, Ohio	B.A.	05/1992	Zoology
Capital University Law School, Columbus, Ohio	certificate	12/2010	Paralegal
Walden University, Minneapolis, MN	M.H.A.	1/2014	Healthcare Administration

A. Personal Statement

I have the expertise, training, and motivation necessary to support the proposed research project. I am a Certified IRB Professional (CIP), with extensive experience in single IRB and SMART IRB initiation. I currently manage the Ohio State IRB program for reliance agreements for researchers conducting multi-site human subjects research. I am Ohio State's SMART IRB point of contact and sit on the Harvard based SMART IRB online reliance system working group to provide user feedback for system design initiatives. Before the SMART IRB online reliance platform was launched, I was instrumental in securing Ohio State's participation in the national SMART IRB master agreement. Prior to joining Ohio State, I served as Director of Research Compliance and Integrity at Nationwide Children's Hospital Research Institute where I provided guidance and monitoring for all research activities including animal research. In that role, I was appointed as a compliance consultant for the IACUC committee. I attended all IACUC meetings and performed annual vivarium inspections as well as IACUC protocol monitoring. Prior to that, I worked as a registered Quality Assurance Professional (RQAP-GLP) while employed for 14 years at Battelle in the laboratory animal resources department. I have extensive experience in both clinical and non-clinical research. My career in research began as a research assistant conducting FDA-regulated animal toxicology studies at Battelle and progressed to Quality Assurance Officer where I performed animal laboratory inspections and study audits. My strong background in animal research and SMART IRB makes my support a unique fit for this project.

B. Positions and Honors

Positions and Employment

1994-1998 Research Technician, Laboratory Animal Resources, Battelle Memorial Institute, Columbus, OH
1998-2008 QA Officer, Biomedical Research Center, Battelle Memorial Institute, West Jefferson, OH
2008-2013 Director, Research Compliance and Integrity, Nationwide Children's Hospital, Columbus, OH
2013-2015 Sr. Compliance Manager, Wexner Medical Center, Ohio State University, Columbus, OH
2015- Program. Manager, Office of Responsible Research Practices, Ohio State University, Columbus OH

Other Experiences and Professional Memberships

1999-2008 Society of Quality Assurance (SQA)
2008-2013 Society of Clinical Research Associates (SOCRA)

2008-2014 Healthcare Compliance Association (HCCA)
2008- Public Responsibility in Medicine & Research (PRIM&R)
2018- Vanderbilt IREx User Feedback Group
2018- Harvard ORS SMART IRB Working Group

Professional Certifications
2017- Certified IRB Professional (CIP)
2011-2013 Certified in Healthcare Research Compliance (CHRC)
2055-2013 Registered Quality Assurance Professional (RQAP-GLP)

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OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ○ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount ($) *Source(s)

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3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Modular Budget

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Budget Period: 1

Start Date: 04/01/2020 End Date: 03/31/2021

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	125,000.00
Consortium Indirect (F&A)	50,000.00
Total Direct Costs*	175,000.00

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	On Campus Organized Research	56.00	125,000.00	70,000.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, 214-767-3261

Indirect (F&A) Rate Agreement Date: 09/23/2016

Total Indirect (F&A) Costs: 70,000.00

C. Total Direct and Indirect (F&A) Costs (A + B)

Funds Requested ($): 245,000.00

Funding Opportunity Number: PAR-19-100. Received Date: 2019-07-08T16:30:17.000-04:00

PHS 398 Modular Budget

Budget Period: 2			
Start Date: 04/01/2021 End Date: 03/31/2022			

A. Direct Costs

	Funds Requested ($)
Direct Cost less Consortium Indirect (F&A)*	150,000.00
Consortium Indirect (F&A)	50,000.00
Total Direct Costs*	200,000.00

B. Indirect (F&A) Costs

	Indirect (F&A) Type	Indirect (F&A) Rate (%)	Indirect (F&A) Base ($)	Funds Requested ($)
1.	On Campus Organized Research	56.00	150,000.00	84,000.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number): DHHS, 214-767-3261

Indirect (F&A) Rate Agreement Date: 09/23/2016

Total Indirect (F&A) Costs: 84,000.00

C. Total Direct and Indirect (F&A) Costs (A + B) Funds Requested ($): 284,000.00

Funding Opportunity Number: PAR-19-100. Received Date: 2019-07-08T16:30:17.000-04:00

PHS 398 Modular Budget

Cumulative Budget Information

1. Total Costs, Entire Project Period

Section A, Total Direct Cost less Consortium Indirect (F&A) for Entire Project Period ($)	275,000.00
Section A, Total Consortium Indirect (F&A) for Entire Project Period ($)	100,000.00
Section A, Total Direct Costs for Entire Project Period ($)	375,000.00
Section B, Total Indirect (F&A) Costs for Entire Project Period ($)	154,000.00
Section C, Total Direct and Indirect (F&A) Costs (A+B) for Entire Project Period ($)	529,000.00

2. Budget Justifications

Personnel Justification	Personnel_Justification1040731551.pdf
Consortium Justification	Consortium_Justification1040731552.pdf
Additional Narrative Justification	

Funding Opportunity Number: PAR-19-100. Received Date: 2019-07-08T16:30:17.000-04:00

Personnel Justification

The Ohio State University

Name	Person Months Effort/Year	Role(s) on Project
Sarah Moore	EFFORT	Dr. Moore is a Diplomate of the American College of Veterinary Internal Medicine, Specialty of Neurology, with 10 years of experience in the field of comparative and translational medicine. She is Director of the OSU CCTS Comparative and Translational Medicine Program and its associated Translational Therapeutics Think Tank. Dr. Moore will oversee all aspects of this project including organization of proposed meetings, generation of reliance documents, REDCap platform construction/modifications, and creation of educational training materials. She will also lead monthly conference calls with the study team to track progress and ensure that milestones are met.
Helen O'Meara		Helen is an associate director in the OSU Office of Responsible Research Practices and has over 13 years of experience in research compliance and regulatory oversight of animal research. She will work with Dr. Moore as a member of the harmonization steering committee to formalize workflow and review processes for the SMART IACUC platform, and will assist with drafting of master agreements.
Ashley Smith		Ashley is a Registered Veterinary Technician who has been a member of the OSU Veterinary Clinical Trials Office for over 8 years. During the past three years she has been responsible for migration of all clinical trial case report forms, associated surveys and clinical trials data bases into REDCap. She has generated a series of libraries within REDCap to support clinical trial efforts. Ashley will be responsible for optimizing the REDCap platform for use as an online reliance system, will assist with development of educational materials, and will provide guidance and training for study team members requiring REDCap technical assistance.
Valerie Bergdall		Dr. Bergdall holds an administrative role associated with regulatory oversight of animal research at OSU. She will provide feedback, on an ad hoc basis, on work flow and master agreements created as part of the project.
Jessica Evans		Jessica holds an administrative role associated with regulatory oversight of human subjects research at OSU. She will provide feedback, on an ad hoc basis, on work flow and master agreements created as part of the project.

Justification for subaward personnel can be found in the *Consortium Justification* attachment.

Consortium Justification

University of Missouri - $117,000

- Year 1 - $58,000
- Year 2 - $59,000

Name	Person Months Effort/Year	Role(s) on Project
Joan Coates	EFFORT	Dr. Coates is a Diplomate of the American College of Veterinary Internal Medicine, Specialty of Neurology, with 20 years of experience in the field of comparative and translational medicine and in the conduct of veterinary clinical trials. She will each serve as a member of the harmonization steering committee to formalize the SMART IACUC workflow and associated master agreements. She will participate in design of education materials and each attend two in-person group meetings and will engage in monthly conference calls to ensure project milestones are met.
Angela McCleary-Wheeler		Dr. McCleary-Wheeler is a Diplomate of the American College of Veterinary Internal Medicine, Specialty of Oncology, with experience in the field of comparative and translational medicine and in the conduct of veterinary clinical trials. She will each serve as a member of the harmonization steering committee to formalize the SMART IACUC workflow and associated master agreements. She will participate in design of education materials and each attend two in-person group meetings and will engage in monthly conference calls to ensure project milestones are met.
Jeff Henegar		Jeff Henegar holds an administrative role associated with regulatory oversight of animal research at University of Missouri. He will serve as a member of the harmonization steering committee to formalize the SMART IACUC workflow and associated master agreements.

Tufts University - $100,000

- Year 1 - $50,000
- Year 2 - $50,000

Name	Person Months Effort/Year	Role(s) on Project
Cheryl London	EFFORT	Dr. London is a Diplomate of the American College of Veterinary Internal Medicine, Specialty of Oncology, with 20 years of experience in the field of comparative and translational medicine and in the conduct of veterinary clinical trials. She will participate in design of education materials and each attend two in-person group meetings and will engage in monthly conference calls to ensure project milestones are met.

David Lee-Parritz	EFFORT	Dr. Lee-Parritz holds an administrative role associated with regulatory oversight of animal research at Tufts. He will serve as a member of the harmonization steering committee to formalize the SMART IACUC workflow and associated master agreements.
Valerie Parkison		Ms. Valerie Parkison holds an administrative role associated with regulatory oversight of animal research at Tufts. He will serve as a member of the harmonization steering committee to formalize the SMART IACUC workflow and associated master agreements.

Brigham & Women's Hospital - $41,000

- Year 1 - $19,000
- Year 2 - $22,000

Name	Person Months Effort/Year	Role(s) on Project
Barbara Bierer	EFFORT	Dr. Bierer will work with the other investigators at OSU, Tufts and Missouri to assist in developing policies and procedures to harmonize regulatory practices between institutions including informed consent; develop training materials for institutions, investigators and staff and minimize regulatory burden. This will require ongoing virtual meetings through phone or video conferencing.

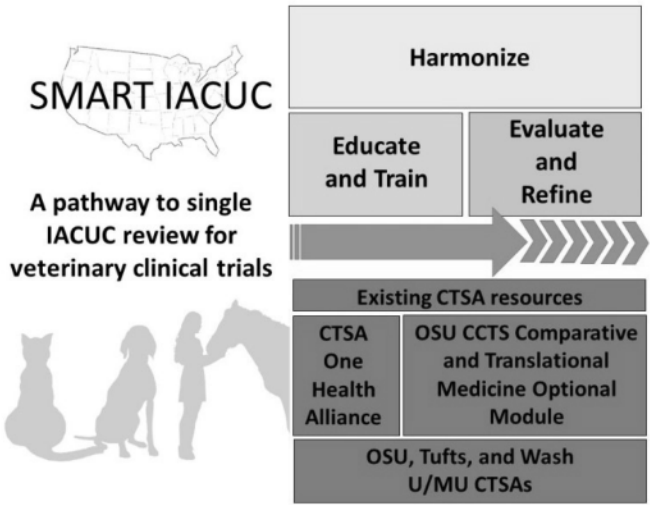
PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	SPECIFIC_AIMS1040731529.pdf
3. Research Strategy*	Research_Plan1040731603.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	Consortium1040731338.pdf
9. Letters of Support	LOS1040731629.pdf
10. Resource Sharing Plan(s)	Resource_Sharing1040731206.pdf
11. Authentication of Key Biological and/or Chemical Resources	
Appendix	
12. Appendix	

SPECIFIC AIMS

Over the past decade there has been increasing interest in incorporating companion animal models of naturally occurring disease, by way of veterinary clinical trials, into pre-clinical therapeutic development with the ultimate goal of optimizing subsequent translational success. However, similar to human clinical trials, implementation of multi-institutional veterinary clinical trials is inefficient due in large part to decentralized processes for trial review, approval and monitoring. Robust and efficient trial evaluation requires an understanding of complex regulatory, scientific, and hospital/ethical issues and must involve individuals experienced in clinical research (IRB-like evaluation) and institutional animal care and use committee (IACUC) representatives with a broad understanding of federal regulatory requirements and guidance. Recently, significant advances have occurred in coordinating veterinary trial performance within the CTSA One Health Alliance (COHA) including formalizing veterinary Good Clinical Practice training, standardizing informed consent processes, and establishing recommendations for trial quality assurance. Our group has been central to these efforts that have enabled several high-impact translational projects, but have also highlighted continued inefficiencies that, once addressed, will ensure that broad integration of veterinary disease models into the therapeutic development process can occur more quickly in order to move the needle of translational science towards success.



A required next step toward achieving that goal is the development of a pathway for single IACUC review of multi-site studies. **We hypothesize that efficiency of veterinary clinical trials can be markedly optimized and enhanced through the design and implementation of a cross-network platform for single review of multi-center veterinary clinical trials called SMART IACUC.** The three CTSA partner institutions included in this application are uniquely positioned to lead this effort given their expertise in veterinary trial design and implementation, ongoing collaborative translational projects, and extensive involvement with COHA and its subcommittees. A co-investigator from Harvard Catalyst ensures the process builds on existing CTSA resources available through the SMART IRB initiative. Lastly, the complementary sets of expertise across partner hubs will be instrumental for successful development and implementation of a harmonized and reliant process for trial review intended for implementation across the larger landscape of COHA and its partners. To accomplish this, we will:

Aim 1: Harmonize veterinary clinical trial review by establishing SMART IACUC. We will convene a group of veterinary clinicians, physicians, and institutional IACUC and IRB officials to establish a "harmonization steering committee" that will customize existing REDCap informatics resources for use as an online reliance system, and will build on Harvard-developed IACUC cross-institutional reliance agreements for purpose-bred animals to develop and execute multi-institutional policies, procedures, and agreements required to facilitate single IACUC review and efficient approval of multi-site veterinary clinical trials.

Aim 2: Educate and train key veterinary clinical trials stakeholders. To ensure broad adoption and successful implementation of our developed mechanism, we will host a training workshop where ethical and regulatory review experts will work with attendees from each of 15 COHA hubs to teach best practices in veterinary trial protocol review and approval, and familiarize them with the SMART IACUC mechanism. A set of online educational materials and FAQs will be developed for use within the CTSA network and beyond.

Aim 3: Evaluate and refine the developed infrastructure using a multi-institutional test case. A test case, consisting of a veterinary clinical trial currently shared across the partner institutions will be processed. We will develop a white paper describing the SMART IACUC initiative, process for implementation, and outcomes from the test case. Test case outcomes will be used to identify opportunities for additional process and infrastructure improvement/refinement prior to broad dissemination of the developed resource to the entire COHA community.

Impact: Implementation of a SMART IACUC platform for veterinary clinical trial review will create a robust, rigorous, and efficient mechanism to support rapid evaluation of novel therapeutics and devices in natural animal models of disease, ultimately encouraging subsequent successful human translation. Once refined, this platform can be disseminated across the COHA network and beyond as a national resource for translational research.

A. SIGNIFICANCE: Successful therapeutic development is markedly hampered by lack of predictive models systems through which to test the efficacy of new treatments. In fact, some diseases (ex. glioblastoma, pancreatic cancer, Alzheimer's disease, spinal cord injury) have experienced few meaningful therapeutic advances despite billions of research dollars spent [1]. Veterinary clinical trials accelerate successful translation and can assist in rapidly identifying ineffective treatments before progression to human clinical trials [2-12]. Recent efforts from our group and the broader CTSA One Health Alliance (COHA) community have laid the ground work for integration of veterinary clinical trials into the therapeutic development pipeline by working to standardize trial processes and resources, and develop guidelines for good clinical practice and informed consent in veterinary clinical research [13]. These efforts and their associated outcomes have substantially enhanced the conduct of single-site trials. They have also facilitated an increase in multi-institutional trials across the veterinary landscape, a trend that will ultimately improve scientific rigor, statistical power and time to study completion.

Despite these important advances, a hurdle to full integration of veterinary clinical trials into the therapeutic development process remains. Presently, institutional animal care and use committees (IACUC) serve, in essence, as veterinary IRBs to review multicenter veterinary clinical trials on a site-by-site basis [14]. Similar to the historical scenario in human medicine, site-specific protocols for approval and monitoring make harmonizing cross-institutional efforts challenging and create inefficiencies and inconsistencies that decrease rigor and reproducibility and increase time to trial completion. To address this hurdle, our proposal aims to build a streamlined platform for single IACUC (sIACUC) review and approval of veterinary clinical trials. Building on the NCATS- driven IRB initiative, we will call this platform SMART IACUC.

Impact: ***The proposed work will allow us to create a platform for efficient and effective multi-site veterinary clinical trial review, leading to seamless and routine integration of natural animal models of disease into the therapeutic development pipeline, ultimately generating an important positive impact on human health by increasing successful translation.*** Once the SMART IACUC mechanism has been established, we will deploy the platform broadly to all COHA institutions and beyond so that uniform, timely approval and initiation of multi-center studies becomes standard across the field.

B. RATIONALE: The pathway of drug development traditionally includes both in vitro and in vivo studies, with in vivo studies almost exclusively involving animal models with induced disease. However, experimental models are often unable to recapitulate the complexity of companion human diseases, may not possess the same physiologic features as natural disease, may require the restriction of additional variables that can influence outcome, and are often deficient at characterizing clinical toxicities and adverse events [1, 18, 23]. While there is no question that experimental animal models are vital to understanding mechanisms of disease and in early-stages of drug development, there is also no shortage of examples where experimental disease models have failed to predict efficacy in human clinical trials [1,3,4]. Substantial translational inefficiencies in therapeutic development underscore the need to integrate new approaches such as the use of natural occurring animal models of disease by way of veterinary clinical trials [16-22].

Current barriers to the conduct of multi-site veterinary clinical trials mirror those present on the human side prior to the development of the Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB, a platform designed to ease common challenges associated with initiating multi-site clinical research that has grown to almost 600 participating institutions since its launch in 2016 [15]. The successful platform, which serves as a central process for participating institutions and their investigators to request, track, and document study-specific reliance arrangements, rather than a central IRB, provides a valuable example from which a parallel veterinary effort can be built.

C. COLLABORATION: This application leverages a multi-institutional and multi-disciplinary team of investigators from four CTSA hubs (The Ohio State University, Tufts, University of Missouri, and Harvard) with both animal and human clinical and regulatory experience who are already engaged with ongoing COHA and translational medicine efforts. **Sarah Moore**, DVM, DACVIM (Neurology), is an Associate Professor at The Ohio State University College of Veterinary medicine (OSU CVM) and will serve as the project leader. She directs the Comparative and Translational Medicine program for the OSU CTSA, and chairs the OSU CVM IACUC subcommittee on privately owned animal studies (veterinary IRB). She is also a member of the COHA Steering Committee, Clinical Studies Subcommittee and One Health Datasets working group, is the faculty lead for an

international research consortium for veterinary clinical trials in spinal cord injury, and is a co-PI on a recently funded R21 evaluating novel therapies to treat neurodegenerative disease using a canine clinical disease model of amyotrophic lateral sclerosis (ALS). She has 10 years of experience leading veterinary clinical research projects with translational impact. **Barbara Bierer**, MD is the faculty director of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center), a Professor of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston and a hematologist/oncologist. She is the Director of the Regulatory Foundations, Ethics and the Law Program of the Harvard Clinical and Translational Science Center and serves as the Director of Regulatory Policy for SMART IRB. She has extensive experience developing and refining the SMART IRB network and has assisted with negotiating regional multi-institutional IACUC reliance agreements for purpose-bred animals. **Cheryl London**, DVM, PhD, DACVIM (Oncology), is a Research Professor at Tufts University, Associate Director of the One Health Program and Director of the Clinical Trials Office at the Tufts Cummings School of Veterinary Medicine. She has an NCI-funded comparative and translational oncology program, chairs the COHA Clinical Studies Subcommittee, and has over 20 years of experience leading clinical trials in veterinary patients. **Joan Coates**, DVM, MS, DACVIM (Neurology), is a Professor at the University of Missouri College Of Veterinary Medicine where she directs the Comparative Neurology Program. Her research focuses on translational therapeutic development for ALS. She has been PI or Co-I on numerous grants leveraging companion animal diseases for translational investigation of biomarkers and therapeutic strategies with funding from NIH/NCATS, NIH/NINDS, Private Source and industrial sponsors. **Angela McCleary-Wheeler**, DVM, PhD, DACVIM (Oncology) is an Assistant Professor at the University of Missouri. A member of the COHA Steering Committee, her research focuses on comparative cancer models using veterinary cancer trials as tools for translational therapeutic development. **David Lee-Parritz** DVM, DACLAM, is a Clinical Professor and Chair of the Department of Environmental and Population Health at Tufts. He also directs the Laboratory Animal Medicine Service and has over 30 years of experience with collaborative animal studies in a wide range of species. He has a diverse background in academic and pharmaceutical biomedical research and a strong commitment to animal model development and refinement. **Valerie Bergdall** DVM, DACLAM, is a board-certified laboratory animal veterinarian, and the Attending Veterinarian for The Ohio State University. She works daily with investigators studying disease in both purpose-bred and client-owned animals and is well-versed in the regulatory requirements associated with animal research. She has also recently worked with Dr. Moore and her colleagues at the OSU Veterinary Medical Center to develop a local process for veterinary clinical trial review that addresses the complex mixture of ethical and regulatory requirements inherent to the use of client-owned (pet) animal subjects in research. **Helen O'Meara** (OSU), **Jeff Henegar** (Missouri), and **Valerie Parkison** (Tufts) each serve in administrative roles within their respective IACUCs and bring expertise in animal subjects-specific regulatory and compliance issues which will be vital to constructing master agreements for cross-institutional reliance. **Jessica Evans** is the program manager for OSU's IRB reliance agreements, provides regulatory support for human clinical trials within the Office of Research, and is active within the SMART IRB initiative at the national level. She has previous experience as a senior compliance manager, quality assurance officer at a major industry partner, and is uniquely suited to contribute to this project because of additional regulatory background related to animal research. She will provide invaluable perspective on what has worked well as an end-use of the SMART IRB platform.

D. INNOVATION: This proposal extends previous COHA and OSU CCTS successes by harnessing the growing momentum within OSU and the COHA consortium driven by cross-institutional partnerships, a previous successful workshop developing best-practice recommendations for veterinary clinical trial review, and an evolving set of high standards for translational veterinary trial infrastructure to address a remaining important hurdle to efficient conduct of multicenter translational veterinary clinical trials: sIACUC review for multi-site studies. In fitting with the R21 mechanism, the project is high-reward in that it's success would create the potential for a future paradigm shift in how promising novel therapeutics are evaluated in the pre-clinical setting. *Specific milestones to be achieved in this proposal are innovative because they represent refinement to the existing process for veterinary clinical trial review and creation and implementation of a new veterinary platform to enable the refined process.*

E. TRANSLATION: The SMART IACUC initiative represents a collaborative effort that engages the broader COHA community at the national level via the COHA Steering Committee (Moore, Coates, London, McCleary-Wheeler, members) and the Clinical Studies (London, Chair; Moore and Coates, members), Communications and Clinician-Scientist Training Subcommittees (See LOS Webb and Trepanier). This wide integration of COHA-associated investigators and efforts ensures that all resources developed will be distributed freely across the

network and rapidly deployed to serve as national resource for improved conduct of veterinary clinical trials (see LOS Meurs).

F. PARTNERSHIPS: The CTSA One Health Alliance (COHA) was established in 2014 as a coalition of academic veterinary centers with CTSA affiliations focusing on One Health/One Medicine activities, particularly those involving comparative research and translational therapeutic development. A core value of COHA is that natural animal models of disease are an important resource that should be used to improve translational efficiency by evaluating promising novel therapies in a veterinary disease setting. The COHA network has grown to include 15 veterinary academic institutions with broad geographic and patient representation, and serves as a platform for multi-institutional partnerships through which veterinary clinical trials can be conducted to study treatments for diseases with significant importance to veterinary and human health. These partnerships have served to extend the reach of comparative medicine strategies, raise awareness of the scientific value of veterinary clinical trials for use in translational therapeutic development, and establish a robust network of veterinary centers committed to improving human and animal health through veterinary clinical research [2, 10, 12]. A recent workshop funded by The Ohio State University CTSA's Comparative and Translational Medicine (CTM) Optional Module was convened with the goals of reconciling local institutional approaches to veterinary clinical trial review and implementation and expanding workforce training for veterinary clinician-scientists poised to make translational impact. Outcomes of this workshop included a veterinary GCP training module, a standardized template for veterinary clinical research consent forms, and a proposed structure for local but standardized ethical and regulatory clinical trial review.

The work proposed in this application builds on recent NCATS success with the establishment of SMART IRB for human clinical trials and cross-institutional reliance agreements for IACUC approval of studies using purpose-bred animals previously developed by Harvard Catalyst and their partner institutions in the Northeast. The inclusion of study team members with extensive animal and human studies regulatory experience and Six Sigma certification ensures that developed processes will be rigorous, efficient, and streamlined, encouraging network-wide adoption.

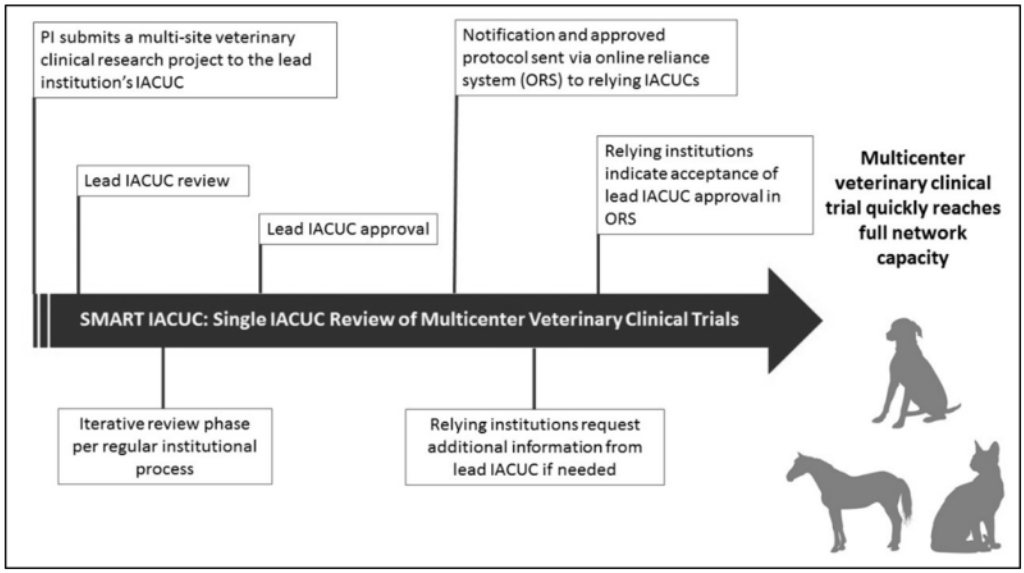
G. BARRIERS: The ethical issues surrounding veterinary clinical trials are complex, and new processes and guidance documents developed will require engagement and agreement from the COHA community as a whole. Additionally, cross-institutional barriers and current discordant processes at academic institutions and across the private sector may make it difficult to reconcile bioethical and regulatory issues without broad input. To address these obstacles, we have convened a diverse project team representing veterinary and human medical specialties, individuals with extensive experience in regulatory and ethical considerations of human clinical trials and animal research, and those with industry background. Additionally, training sessions proposed in Aim 2 and designed to include representatives from every COHA institution will allow us to obtain additional input on the new platform and will facilitate buy-in. Lastly, as with SMART IRB, the platform (using REDCap as the portal) will be designed to be intentionally iterative and sufficiently flexible to respond to evolving needs of the translational research community.

H. RESEARCH APPROACH: The proposed project will build on substantial progress in the field of veterinary clinical trials by leveraging existing COHA and CTSA resources to create a singular process for veterinary multicenter trial review and implementation, paralleling recent successful efforts with human IRBs, to improve efficiency and rigor of veterinary clinical trial review, conduct, and ultimate use in translational efforts (Fig 1).*We hypothesize that efficiency of veterinary clinical trials can be markedly optimized and enhanced through the design and implementation of a cross-network platform for single review of multi-center veterinary clinical trials called SMART IACUC***.** We will evaluate this hypothesis through the following aims:

Aim 1: Harmonize veterinary clinical trial review by establishing SMART IACUC.
Rationale: Presently, veterinary clinical trial review and approval in multicenter trials is managed on a site-by-site basis by local IACUCs essentially serving as veterinary IRBs. For multi-site studies, the need for multiple local IACUC approvals creates inconsistencies in trial review, and substantially delays reaching full functional capacity across sites. To address the need for robust, consistent, and efficient trial review and initiation in veterinary medicine, we have recently developed an informed consent template for use in veterinary clinical trials across COHA hubs, and have worked locally to develop a robust review process at OSU that encompasses all aspects of regulatory and ethical/hospital factors uniquely inherent to translational health research in client-

owned animals. We have also served in a consulting role, advising on the local implementation of a similar structure at partner institutions. This work was directly supported by the OSU CTM Optional Module associated with the OSU Center for Clinical and Translational Sciences (OSU CCTS) recently renewed CTSA award. Building on our recent progress toward local but congruent review processes, we propose to extend this work to two other COHA institutions active in veterinary clinical trials to establish a standardized workflow and reliance system for sIACU review and approval of multi-site trials. In parallel to the human trials initiative, we will call our platform SMART IACUC. While this project initially proposes to establish our platform across three CTSA/COHA partner institutions, the ultimate goal is to develop a set of harmonized processes, best practices, and a system for cross-institutional IACUC reliance that can be broadly disseminated to all CTSA hubs and beyond. Of particular importance will be the development of an online reliance system (ORS) that will simplify the selection of a single lead IACUC for review of multi-site studies, will allow management of communications across lead and relying institutions, will track the status of reliance requests, will document reliance agreements on a study-by-study basis, and will provide summary reports and tracking mechanisms for individual institutions serving as reviewing and reliant institutions for an individual study.

Figure 1. Proposed workflow for a national SMART IACUC platform for single IACUC review of multi-site veterinary clinical trials.



Methods: To effectively address the governance and technical needs required for sIACUC review of multi-site veterinary clinical trials, we will establish a "harmonization steering committee" to develop a strategic, cooperative, and efficient approach. The group will be composed of clinicians, IACUC administrative and institutional regulatory staff, and technical staff from each of the three veterinary partner institutions and will develop policies and procedures, workflow, and review and implementation guidance documents that can be shared broadly across and outside of the network. Specifically, the committee will complete the following activities:

a. Establish a network of partnering institutions to serve as the foundation of the SMART IACUC effort. OSU, Tufts, and Missouri are already partnering, via OSU CTM and COHA-related efforts, to standardize their local clinical trial review processes. To enhance the impact of these individual efforts, we will create a more structured and centralized approach by developing a sIACUC platform for multi-site trials which we will call SMART IACUC. These institutions are uniquely positioned to serve as the foundation for a SMART IACUC effort because of their complimentary expertise in veterinary clinical trial design and regulatory oversight, and their current portfolio of overlapping multi-site trials. We will convene an inaugural SMART IACUC workshop to delineate key infrastructure requirements necessary for facilitating success and will develop a cohesive framework for evaluating, approving, and monitoring veterinary multi-site clinical trials such that reliance can be granted between participating institutions. We will leverage expertise currently available within Harvard Catalyst with respect to both animal and human IRB reliance agreements and multi-site approval processes.

b. Create master agreements. Master agreements are a necessary step toward a national IACUC reliance system. These agreements will ensure sIACUC reviews meet the regulatory requirements for, and govern the technical aspects of, veterinary trial review. Our group will leverage expertise from the human SMART IRB initiative, coupled with institutional know-how on the IACUC regulatory side to develop and execute key multi-institutional master agreements that enable reliance. Reliance and other master agreements will be drafted using existing Harvard Catalyst documents in use for regional multi-institutional reliance for IACUC approval of purpose-bred animal studies.

c. Modify the currently existing REDCap platform to serve as a central portal for the SMART IACUC platform. We will develop forms within REDCap that will support an online reliance system (ORS) and central portal through which network sites can request, track, and document study-specific reliance arrangements, maintain connectivity, report adverse events, and perform data transfer**.** We have selected REDCap as our proposed ORS because it offers sufficient flexibility in data management such that customized study application forms and user groups required to sustain this project long-term can be easily accommodated, it is open source, and it is already supported at all COHA institutions. Funding from the OSU CTSA and a previously awarded administrative supplement have already supported a two-day intensive REDCap training workshop for participants from all 15 COHA member institutions, facilitating broad adoption of the REDCap platform across hubs. The partner sites will work together to develop and optimize forms and features within the platform, allowing institutions to request to join the SMART IACUC network, facilitating required administrative processes, allowing requests for reliance, and for reliance requests to be examined and approved by partner institutions.

Aim 2: Educate and train key stakeholders to ensure broad adoption and success.
Rationale: Currently, expertise and resources related to veterinary clinical trial review are housed at individual institutions. Consequently, there is no centralized mechanism for developing and distributing these materials, or for training researchers, clinicians, and institutional representatives in the complex regulatory, scientific, and hospital/ethical issues associated with veterinary clinical trials. This process must involve individuals experienced in veterinary clinical studies (IRB-like evaluation) and institutional animal care and use committee (IACUC) representatives with a broad understanding of federal regulatory guidance and requirements. Wide-scale adoption of the sIACUC reliance system developed in Aim 1 will require training for all COHA hubs interested in joining the developed platform.
Methods: To facilitate broad dissemination of currently existing local expertise in veterinary clinical trial review, and to extend the impact of the SMART IACUC network, we will develop and deliver a library of resources and comprehensive training tools focusing on best practices for veterinary clinical trial review and implementation and on logistical aspects of the SMART IACUC system for review of multi-site trials. This effort will consist of both in-person and online training opportunities focused on veterinary clinical trial review and approval. The process will be iterative, with opportunities to adjust the structure and content of the training materials based on trainee feedback throughout the process and based on investigator and staff feedback as collected in Aim 3.
a. Design and deliver an in-person training session. This session will be hosted and presented by the members of the SMART IACUC “harmonization steering committee” and will focus on a breadth of topics vital to standardized review and conduct of trials, including best practices in veterinary clinical study evaluation and IACUC regulatory requirements, standardized approaches to informed consent, adverse event monitoring and reporting, and specific technical aspects of the SMART IACUC platform and the REDCap ORS. This session will be open to attendees from all 15 COHA institutions and will consist of a one-day in-depth training course with a second day devoted to involving attendees in the construction of online training materials to ensure that the topics covered are optimized for understanding and are available for broad distribution across hubs.
b. Develop online training modules. A primary goal of the SMART IACUC initiative is to facilitate sharing and utilization of educational materials for dissemination across the network and beyond. To this end, we will develop, in cooperation with attendees in Aim 2a, a series of online training resources. These will be housed on the COHA website, which has recently been updated as part of a Tufts CTSI administrative supplement to facilitate access by an ever-growing number of COHA member institutions committed to high quality veterinary clinical trials as translational tools. These open-access web resources will address relevant aspects of the SMART IACUC process and key requirements for a harmonized approach to veterinary clinical trial review. Planned topics include an introduction to SMART IACUC and the REDCap ORS; responsibilities of reviewing and relying institutions; resources for IACUC personnel; and information about implementing reliance agreements.

Aim 3: Evaluate and refine the developed infrastructure via a multi-institutional test case.
Rationale: The SMART IACUC platform represents an unprecedented effort across the veterinary clinical trials community to promote uniformity and efficiency in trial review and implementation in order to enhance the utilization of natural animal diseases in translational research. While the ultimate goal is national adoption of the SMART IACUC platform for all multicenter trials, refinement on a regional level is a prerequisite. To identify opportunities for additional process and infrastructure improvement prior to broader implementation of the platform, we will evaluate a multi-institutional test case by processing a veterinary clinical trial currently shared across OSU, Missouri, and Tufts Veterinary Medical Centers.

Methods: NCATS R21R002277 (mPI Coates and Moore) is a veterinary clinical trial involving investigators from all three partner institutions. The study employs a novel adaptive platform clinical trial design for evaluating translational therapies in a canine disease model of ALS. As a perpetual trial, new treatments are expected to come in to the study at regular intervals, providing opportunity for use as a test-case to evaluate metrics before and after implementation of a sIACUC review process. Each partner institution currently holds or is in the process of obtaining its own local IACUC-approved protocol for the trial, but we will create a parallel sIACUC instance to test and refine our new process. The project will be submitted and reviewed via the SMART IACUC mechanism and will be used to highlight what is working well and where the SMART IACUC process can be improved to enhance broad adoption and success. We will complete the following activities:

a. Collect metrics for standard versus sIACUC review of a veterinary trial shared across institutions. Specifically, we will calculate and compare the time to full functionality (approval at all three partner sites) for both the standard and sIACUC approaches. We will also compare "number of touches" to approval, defined as the number of times the protocol changes hands, to assess process efficiency. Lastly, we will evaluate the number of times reliance agreements are returned, prior to approval, to the initiating institution for clarifications, data errors, requests for more information, etc. in order to assess and refine sIACUC ORS agreements and forms.

b. Design and distribute a post-approval survey to obtain feedback from key stakeholders. A REDCap-based survey will be designed and distributed after the final sIACUC approval of the test case to principal investigators, IACUC staff and committee members, and any other key stakeholders identified during the development of the SMART IACUC initiative to assess their overall satisfaction with the new sIACUC process, obtain their feedback on pain points, and document opportunities for continued process refinement.

c. Draft and publish a white paper describing the SMART IACUC development process. We will use this manuscript to document and disseminate the SMART IACUC platform and to provide background and justification for a national approach to sIACUC review of multi-site veterinary trials. We will also report standard versus sIACUC metrics for the test case as a measure of efficiency and impact of the new process and will include feedback and opportunities for refinement as identified during post-approval stakeholder surveys.

2.4 Milestones and future directions: The following milestones will be met over the 24 months of funding associated with this supplement:

Aims	Benchmarks of Success	Outcome
Establish SMART IACUC	• Convene steering committee • Create master agreements • Create REDCap forms • Implementation of REDCap ORS across 3 partner sites	• Uniform and seamless veterinary clinical trial approval across centers
Educate and train stakeholders	• Conduct in-person training session • Create 4 online training modules	• Acceptance of and engagement with the SMART IACUC process across COHA institutions and beyond
Evaluate and refine the network	• Complete sIACUC review and approval of a multi-institutional test-case • Compare "before" and "after" metrics • Publish post-approval white paper	• Fully refined platform ready to be deployed as a national resource

The purpose of this proposal relates to our long-term goals of formalizing existing comparative and translational medicine efforts across CTSA hubs; optimizing methods and processes for veterinary clinical trials; and promoting resource sharing. These goals can only be optimally achieved by taking a collaborative approach. Successful completion of the aims, as defined above, will create a platform for efficient and effective veterinary clinical trial review and for harmonization of processes across COHA centers, a hurdle which must be cleared for seamless integration of veterinary disease models into the therapeutic development pipeline. Once the SMART IACUC mechanism has been established and evaluated across the partner institutions in this proposal, we will work to build a larger network of reliant institutions such that the effort can be disseminated as a national resource for translational research, resource sharing, and collaboration and engagement.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	❍ Yes ● No
Is the Project Exempt from Federal regulations?	❍ Yes ❍ No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Does the proposed research involve human specimens and/or data	❍ Yes ● No
Other Requested information	

REFERENCES

1. Hay, M., Thomas, D. W., Craighead, J. L., Economides, C. & Rosenthal, J. Clinical development success rates for investigational drugs. Nat Biotechnol 2014. 32: 40-51

2. Paoloni M, Khanna C. Translation of new cancer treatments from pet dogs to humans. Nature reviews Cancer 2008. 8:147-56.

3. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004. 3: 711-715.

4. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development: success rates for investigational drugs. Clin Pharmacol Ther 2010. 87: 272-277.

5. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennesy L, Finnerty CC, Lopez CM, Honari S, Moore EE, Minei JP, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A 2013. 110: 3507-3512.

6. London CA, Bear MD, McCleese J, Foley KP, Paalangara R, Inoue T, Ying W, Barsoum J. Phase I Evaluation of STA-1474, a Prodrug of the Novel HSP90 Inhibitor Ganetespib, in Dogs with Spontaneous Cancer. PLoS One 2011. 6: e27018.

7. London CA, Bernabe LF, Barnard S, Kisseberth WC, Borgatti A, Henson M, Wilson H, Jensen K, Ito D, Modiano J, Bear MD, Pennell ML, Saint-Martin JR, McCauley D, Kauffman M, Shacham S. Preclinical evaluation of the novel, orally bioavailable Selective Inhibitor of Nuclear Export (SINE) KPT-335 in spontaneous canine cancer: results of a phase I study. PLoS One 2014. 9: e87585.

8. Kol A, Arzi B, Athanasiou KA, Farmer DL, Nolta JA, Rebhun RB, Chen X, Griffiths LG, Verstraete FJ, Murphy CJ, Borjesson DL. Companion animals: Translational scientist's new best friends. Science translational medicine 2015. 7:308ps21.

9. Gurda BL, De Guilhem De Lataillade A, Bell P, Zhu Y, Yu H, Wang P, Bagel J, Vite CH, Sikora T, Hinderer C, Calcedo R, Yox AD, Steet RA, Ruane T, O'Donnell P, Gao G, Wilson JM, Casal M, Ponder KP, Haskins ME. Evaluation of AAV-mediated Gene Therapy for Central Nervous System Disease in Canine Mucopolysaccharidosis VII. Molecular therapy: The Journal of the American Society of Gene Therapy 2016. 24:206-16.

10. LeBlanc AK, Mazcko C, Brown DE, Koehler JW, Miller AD, Miller CR, Bentley RT, Packer RA, Breen M, Boudreau CE, Levine JM, Simpson RM, Halsey C, Kisseberth W, Rossmeisl JH, Jr., Dickinson PJ, Fan TM, Corps K, Aldape K, Puduvalli V, Pluhar GE, Gilbert MR. Creation of an NCI comparative brain tumor consortium: informing the translation of new knowledge from canine to human brain tumor patients. Neuro-oncology 2016. 18:1209-18.

11. Gurda BL, Bradbury AM, Vite CH. Canine and Feline Models of Human Genetic Diseases and Their Contributions to Advancing Clinical Therapies. The Yale J of biology and Med 2017. 90:417-31.

12. Moore SA, Granger N, Olby NJ, Spitzbarth I, Jeffery ND, Tipold A, Nout-Lomas YS, da Costa RC, Stein VM, Noble-Haeusslein LJ, Blight AR, Grossman RG, Basso DM, Levine JM. Targeting

Translational Successes through CANSORT-SCI: Using Pet Dogs to Identify Effective Treatments for Spinal Cord Injury. J Neurotrauma 2017. 15: 2007-2018.

13. Sobolewski J, Bryan JN, Duval D, O'Kell A, Tate DJ, Webb T, Moore SA. Readability of consent forms in veterinary clinical research. J Vet Internal Med 2019. 33: 350-355.

14. Page R, et al. Conduct, Oversight, and Ethical Considerations of Clinical Trials in Companion Animals with Cancer: Report of a Workshop on Best Practice Recommendations. J Vet Intern Med 2016. 30:527-35.

15. https://smartirb.org/resources/. Accessed July 1, 2019.

16. Paoloni M, Lana S, Thamm D, Mazcko C, Withrow, S. The creation of the Comparative Oncology Trials Consortium Pharmacodynamic Core: Infrastructure for a virtual laboratory. Vet J 2010. 185: 88-89.

17. Paoloni, M, Webb C, Mazcko C, Cherba D, Hendricks W, Lana S, Ehrhart EJ, Charles B, Fehling H, Kumar L, Vail D, Henson M, Childress M, Kitchell B, Kingsley C, Kim S, Neff M, Davis B, Khanna C, Trent J. Prospective molecular profiling of canine cancers provides a clinically relevant comparative model for evaluating personalized medicine (PMed) trials. PLoS One 2014. 9: e90028.

18. Paoloni, MC, Mazcko C, Fox E, Lana S, Kisseberth W, Vail DM, Nuckolls K, Osborne T, Yalkowsky S, Gustafson D, Yu U, Cao L, Khanna C. Rapamycin pharmacokinetic and pharmacodynamic relationships in osteosarcoma: a comparative oncology study in dogs. PLoS One 2010. 5: e11013.

19. Levine JM, Cohen ND, Fandel TM, Levine GJ, Mankin J, Griffin JF, Kerwin SC, Boudreau CE, Trivedi A, Noble-Haeusslein LJ. Early blockade of matrix metalloproteinases in spinal cord-injured dogs results in long-term increase in bladder compliance. J Neurotrauma 2017. 34: 2656-2667.

20. Hu Hz, Granger N, Pai SB, Bellamkonda RV, Jeffery ND. Therapeutic efficacy of microtube-embedded chondroitinase ABC in a canine clinical model of spinal cord injury. Brain 2018. 141: 1017-1027.

21. Beltran WA, Cideciyan AV, Lewin AS, Iwabe S, Khanna H, Sumaroka A, Chiodo VA, Fajardo DS, Roman AJ, Deng WT, Swider M. Aleman TS, Boye SL, Genini S, Swaroop A, Hauswirth WW, Jacobson SG, Aquirre GD. Gene therapy rescues photoreceptor blindness in dogs and paves the way for treating human X-linked retinitis pigmentosa. Proc Natl Acad Sci U S A 2012. 109: 2132-2137.

22. Kwon BK, Streijger F, Hill CE, Anderson AJ, Bacon M, Beattie MS, Blesch A, Bradbury EJ, Brown A, Bresnahan JC, Case CC, Colburn RW, David S, Fawcett JW, Ferguson AR, Fischer I, Floyd CL, Gensel JC, Houle JD, Jakeman LB, Jeffery ND, Jones LA, Kleitman N, Kocsis J, Lu P, Magnuson DS, Marsala M, Moore SW, Mothe AJ, Oudega M, Plant GW, Rabchevsky AS, Schwab JM, Silver J, Steward O, Xu XM, Guest JD, Tetzlaff W. Large animal and primate models of spinal cord injury for the testing of novel therapies. Exp Neurol 2015. 269: 154-168.

CONSORTIUM/CONTRACTUAL ARRANGEMENTS

This proposal is a collaborative effort between The Ohio State University (OSU), University of Missouri (MU), Tufts University, and Harvard. OSU will serve as the prime institution for the project and MU, Tufts and Harvard will serve as sub recipients. All four institutions are CTSA institutions as defined in the funding opportunity announcement. The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

OSU is the logical choice to be the applicant organization because OSU Associate Professor, Dr. Sarah Moore, has led substantial local efforts to revise, streamline, and improve regulatory review of veterinary clinical trials. She also has a 10 year track record of conducting veterinary clinical research on the translational spectrum, directs the Comparative and Translational Medicine Optional Module through OSU's CTSA, and is the chair of OSU's IACUC Privately Owned Animals Subcommittee (vet IRB). The Co-investigators will each bring their own expertise in this collaborative investigation to develop the proposed SMART IACUC platform and to ensure its dissemination and deployment across the COHA network.

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Professor of Medicine, Harvard Medical School
Director, Regulatory Foundations, Ethics and the Law Program
Director of Regulatory Policy, SMART IRB
Harvard Catalyst | The Harvard Clinical and Translational Science Center

Email: bbierer@bwh.harvard.edu

Sarah Moore, DVM, Diplomate ACVIM (Neurology)
Director, CCTS Comparative and Translational Medicine Program
Associate Professor, Neurology and Neurosurgery
Co-director, Clinical and Translational Neurology Laboratory
College of Veterinary Medicine Department of Veterinary Clinical Sciences
Veterinary Medical Center , 601 Vernon L. Tharp St. , Columbus , OH 43210

July 3, 2019

Dear Dr. Moore,

Please accept this letter written in enthusiastic support of your application "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). I am excited to collaborate with you on this important project. As you know, I am the Director of Regulatory Policy, SMART IRB, a system of national reliance for institutional review boards (IRBs) for human participant protections that we developed over the past many years. We have developed significant resources and tools, and a Joinder system, that I believe will be helpful for you to leverage for the proposed project, dedicated to enhancing the review and approval process for multi-site veterinary clinical trials. Further, we developed, and I have shared with you, the Harvard IACUC reliance agreement and appendix that I hope will serve as a starting point for your work.

I am the Director of the Regulatory Foundations, Ethics and the Law Program of the Catalyst | The Harvard Clinical and Translational Science Center, and have previously served as senior vice president for research at the Brigham and Women's Hospital and as the institutional official for human participant and animal research, biosafety, and research integrity. I am well aware of the need for operational improvements to our current approach of individual institutional review, and of the burden that this approach places on investigators and institutions. We must improve efficiencies particularly as interinstitutional collaboration is increasing. The SMART IACUC system that you propose will do so; it is critically important for translational research that involves preclinical animal disease models. While building infrastructure to ensure compliance, it is essential to maintain the highest levels of ethical review and oversight. Your proposal

has considered each of these elements, and I am honored to share our experience and resources with your team to help deliver a successful system.

I would be delighted to answer additional questions or provide further information.

I wish you every success with your application.

Best regards,

Personal Signature

Barbara E. Bierer, MD

Director of Regulatory Policy, SMART IRB
Director, Regulatory Foundations, Ethics and the Law Program
Harvard Catalyst | The Harvard Clinical and Translational Science Center

Professor of Medicine, Harvard Medical School

Senior Physician, Division of Global Health Equity
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June 26, 2019

Sarah Moore DVM
The Ohio State University
601 Vernon Tharp Street
Columbus, OH 43210

Dear Dr. Moore,

Please accept this letter of strong support for your proposal, entitled “SMART IACUC: A path to harmonized veterinary multi-site trial review” submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). As the Director of Animal Care Quality Assurance and the Office of Animal Resources at the University of Missouri, I am committed to the humane care and use of animals in research and teaching, and to adhering to applicable laws, principles, standards, guidelines and policies affecting such use. As such, I am pleased to serve as a co-investigator on this project and to provide insight and input from my institution’s perspective on how to best harmonize veterinary clinical trial review across COHA sites.

I look forward to working together on this new project and commit to providing feedback and guidance from a regulatory perspective with respect to animal use guidelines and their applicability to veterinary clinical research. I wish you success with this application and am excited to work with you on the described projects.

Sincerely,

Personal Signature

Jeff Henegar, Ph.D.

University of Missouri

College of Veterinary Medicine
Veterinary Health Center
900 E Campus Drive
Columbia, MO. 65211
PHONE 573-882-7821

June 26, 2019

Dear Dr. Moore,

This letter is written in enthusiastic support of your proposal, entitled *"SMART IACUC: A path to harmonized veterinary multi-site trial review"* submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). As a veterinary neurologist and neurosurgeon by training, and as an NIH-funded translational scientist, I am keenly aware of the value of veterinary disease models for translational therapeutic development. I have a long track record of conducting clinical research in the veterinary setting and thus also have a good understanding of the current hurdles and barriers to efficient multi-center trial review and conduct.

Our research interests complement very well. Specifically, I am heavily involved in the Comparative Neurology Program, a research program that explores inherited developmental and degenerative diseases—we specifically aim to understand the underlying molecular pathogenesis and relate our findings to corresponding diseases in humans. My main endeavor is to translate our understanding into improved diagnostic and therapeutic strategies for both dogs and people. I have been studying canine degenerative myelopathy for over 20 years. As you know, we have collaborated on several clinical research projects over the years, including co-mentorship of a veterinary resident/graduate student. We also work together on several on-going projects including serving as co-PIs on an NCATS-funded R21 that works to build a multi-center veterinary trial platform in the context of a natural disease model of ALS.

Based on our shared experience with our current R21, it is clear to me that the work proposed here is important and vital to move the translational needle in the context of veterinary clinical trials. I am excited about our continued collaboration on this new project and commit to serving as a co-investigator. I will provide input from a clinician's perspective on the logistics of veterinary clinical trial review and implementation, with a specific focus on efficiency and rigor. I wish you the best of luck with this application and look forward to working on this project together.

Sincerely,

Personal Signature

Joan R. Coates, DVM, MS, Diplomate ACVIM (Neurology)
Professor, Veterinary Neurology & Neurosurgery
Section Head Neurology & Neurosurgery
Department of Veterinary Medicine and Surgery

University of Missouri

College of Veterinary Medicine
Veterinary Health Center
900 E Campus Drive
Columbia, MO. 65211
PHONE 573-882-7821

June 26, 2019

Dear Dr. Moore:

Please accept this letter written in strong support of your proposal, entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). My background as both a research scientist and a clinical veterinary oncologist makes me uniquely passionate about the use of veterinary disease models as translational tools for therapeutic development. My work as a veterinary clinician has provided the opportunity to participate at the national level on several multi-institutional research collaborations, including the NCI-funded Comparative Oncology Trials Consortium and various CTSA One Health Alliance (COHA) initiatives.

The study proposed in this application addresses many of the current barriers to efficient use of veterinary disease models in translational research. Specifically, lack of a harmonized approach to trial review and implementation leads to substantial inefficiencies in trial conduct and can reduce rigor. As you know, we have collaborated previously on various COHA endeavors at the national level, and have a strong track record of working together in both the clinical and consortium settings. I am pleased to serve as a co-investigator on this project to provide input from a clinician's perspective on the logistics of veterinary clinical trial review and implementation and to work with others at my institution to facilitate acceptance of new processes developed as part of this initiative. As the chair of the COHA Strategic Planning working group, and as my institutional representative to the COAH Steering Committee, I help to ensure broad dissemination of all developed resources and processes across the COHA community and beyond. I wish you the best of luck with this proposal.

Sincerely,

Personal Signature

Angela L. McCleary-Wheeler, DVM, PhD, DACVIM (Oncology)
Assistant Professor, Section of Oncology
Department of Veterinary Medicine and Surgery
College of Veterinary Medicine
University of Missouri
mcclearywheelera@missouri.edu

Tufts UNIVERSITY Cummings School of Veterinary Medicine

June 26, 2019

Dear Dr. Moore,

Please accept this letter written in strong support of your proposal, entitled “SMART IACUC: A path to harmonized veterinary multi-site trial review” submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). As you know, I am a veterinary oncologist by training and have a long-standing commitment to the use of veterinary disease models as a tool to advance translational therapeutic development efforts. My involvement in a variety of multi-institutional research collaborations, including the Comparative Oncology Trials Consortium and the NCI-funded Canine Brain Tumor Consortium have highlighted the need for a harmonized and efficient approach to multi-site veterinary trial review and implementation, in order to enhance the integration of veterinary disease models more fully into the translational research pipeline.

The work you describe in this application represents an important step toward the long-term goal of both myself and the CSTA One Health Alliance (COHA) community, which is to leverage naturally occurring diseases of veterinary patients as models to improve translational efficiency in health research. You and I have collaborated on a variety of projects over the last ten years, including working together as study team members on an active NIH-funded R21, and participating in several COHA committees and working groups together at the national level. I look forward to continuing to work together on this new project and commit to serving as a co-investigator. I will provide input from a clinician’s perspective on the logistics of veterinary clinical trial review and implementation. Additionally, as the chair of the COHA Clinical Studies Subcommittee, I will work to help disseminate all developed resources and processes across the COHA community and beyond.

Sincerely,

Personal Signature

Cheryl London DVM PhD DACVIM (oncology)
Anne Engen and Dusty Professor
Director, Clinical Trials Office
Cummings School of Veterinary Medicine
Tufts University

Tufts UNIVERSITY

Office of the Vice Provost for Research

June 26, 2019

Dear Dr. Moore,

I write this letter to confirm my enthusiastic support for your proposal, entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). I am pleased to serve as a co-investigator on this project and to provide insight and input from my own background and my institution's perspective on how to best harmonize veterinary clinical trial review across COHA sites and how to develop a single review process for multi-site veterinary clinical trials. Your proposed work is important because it will improve the rigor and efficiency of veterinary clinical research and beyond that, will facilitate better integration of natural animal models of disease into translational research efforts.

As the regulatory compliance director at Tufts University and Tufts Medical Center, I have 19 years of experience working in the regulatory environment for the use of animals in research, teaching, and training. I have a strong track record of creating efficiencies to ensure compliance while also serving to minimize administrative burden. Therefore, I offer a broad range of experience with research regulations and institutional solutions. I look forward to working with you on this project and wish you every success with your application.

Sincerely,

Personal Signature

Valerie Parkison, MS, CPIA
Regulatory Compliance Director
Office of the Vice Provost for Research
Tufts University
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Cummings School
of Veterinary Medicine

Department of Environmental
and Population Health

June 26, 2019

Dr. Sarah Moore DVM, DACVIM
Director, CCTS Comparative and Translational Medicine Program
The Ohio State University - College of Veterinary Medicine
Veterinary Medical Center
601 Vernon L. Tharp St. , Columbus , OH 43210

Dear Dr. Moore,

Please accept my strong support, as indicated in this letter, for your project, entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). I am very pleased to serve as a co-investigator on this project. With 30 years' experience in the care of research animals, and because of my training as a laboratory animal veterinarian, I am widely recognized as an expert collaborator for faculty and staff on innovative solutions to complex scientific and logistical challenges such as the ones dealt with in this proposal. My diverse background in academic and pharmaceutical biomedical research also allows me to bring insight from the industry perspective which can further strengthen the project. I look forward to collaborating on this important project and commit to working together toward completion of the aims and to providing guidance from a regulatory perspective with respect to animal use guidelines and their applicability to veterinary clinical research both locally at Tufts University, and across the COHA network. Best of luck with your application and I am excited to move forward with this work.

Sincerely,

David Lee-Parritz DVM, DACLAM
Clinical Professor and Chair

200 Westboro Road, North Grafton, MA 01536 | TEL: 508.887.4341

THE OHIO STATE UNIVERSITY

Office of Research

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June 28, 2019

Dear Dr. Moore,

Please accept this letter in strong support of your application “SMART IACUC: A path to harmonized veterinary multi-site trial review” submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). As the Associate Director of The Ohio State University’s IACUC/IBC, I am well positioned to serve as a collaborator on this important project, which serves to develop a new approach for reviewing veterinary clinical trials. With over 13 years of experience providing leadership for the administrative, regulatory and programmatic activities supporting OSU’s animal research program, I am interested in improving efficiencies for regulatory reviews and reducing regulatory burdens. Prior to my current role, I had over 10 years leading animal toxicology studies and preparing assessments required by regulatory agencies for the registration of new products. I have presented IACUC regulatory requirements in presentations both locally and at national conferences for IACUC administrators. I have also worked in close collaboration with other IACUC administrators as part of the Big Ten Academic Alliance IACUC Administrators subgroup in sharing best practices. As you know, we have worked closely together to streamline and improve the review process for veterinary clinical trials at OSU, and have consulted with other universities interested in mirroring our processes.

The work proposed in this grant represents an important next step toward rigorous and uniform review of veterinary clinical trials and I am pleased to work with your team to help them move forward with this much-needed work. I am happy to assist with and provide input for the development of the SMART IACUC mechanism and will provide formative feedback on guidance documents and reliance agreements. I wish you the best of luck with your grant application and look forward to working with you on this project.

Sincerely,

Personal Signature

Helen O’Meara, M.S., CPIA
Lean Six Sigma Green Belt
Associate Director, IACUC/IBC

THE OHIO STATE UNIVERSITY

Office of the Attending Veterinarian

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July 3, 2019

Dear Dr. Moore,

Please accept this letter written in enthusiastic support of your project, entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). As the Director of the University Laboratory Animal Resources and the Institutional Attending Veterinarian at The Ohio State University, I am keenly aware of the critical need to harmonize veterinary clinical trial review processes across veterinary medical institutions in order to promote robust, collaborative, and efficient translational science while promoting best practices in research using client-owned animals.

As you know, we have worked together previously at the institutional level to streamline our institutional review of veterinary clinical trials and have served together on OSU's Institutional Animal Care and Use Committee. I look forward to our continued collaboration on this new project and commit to providing feedback and guidance from a regulatory perspective with respect to animal use guidelines and their applicability to veterinary clinical research. I wish you success with this application and am excited to work with you on the described projects.

Sincerely,

Personal Signature

Valerie Bergdall

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July 5, 2019

Dr. Sarah Moore
The Ohio State University
Department of Veterinary Clinical Sciences
601 Vernon L Tharp St.
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Re: Letter of Support for "SMART IACUC"

Dear Dr. Moore,

Please accept this letter in strong support of your application "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). I am excited to collaborate with you on this important project and can commit to working with your group to bring my experience with the SMART IRB so that the proposed project can leverage this existing CTSA resource to and build upon it to enhance the review and approval process for multi-site veterinary clinical trials. As you know, I currently manage the Ohio State IRB program for reliance agreements for researchers conducting multi-site human subjects research. I am also Ohio State's SMART IRB point of contact and sit on the Harvard based SMART IRB online reliance system working group to provide user feedback for system design initiatives. In addition to my background in human subjects approvals, I also have a background in animal studies, having served as Director of Research Compliance and Integrity at Nationwide Children's Hospital Research Institute where I provided guidance and monitoring for all research activities including animal research. In this role, I became familiar with IACUC policies and procedures. Prior to that, I worked as a registered Quality Assurance Professional (RQAP-GLP) while employed for 14 years at Battelle in the laboratory animal resources department. Because of my unique background in both animal and human subjects work, coupled with both academic and industry experience, I believe I can serve as a uniquely qualified collaborator on the work proposed in this application. I am excited to work with your team to move the project forward and wish you success with your proposal.

Sincerely,

Personal Signature

Jessica Evans, MHA, CIP

Program Manager
Reliance Agreements & Regulatory Support
Office of Responsible Research Practice
The Ohio State University
1960 Kenny Road Columbus, OH 43210-1063

Cc: Kim Toussant, HRPP Director

THE OHIO STATE UNIVERSITY
CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

Center for Clinical and Translational Science

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June 17, 2019

Dear Scientific Review Committee,

As the PI on The Ohio State University's Clinical and Translational Sciences award, I am pleased to provide this letter of support for the project entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). This project embodies the purpose set out by this FOA as a highly innovative, exploratory collaborative research project developed by three institutions with NIH CTSA programs: The Ohio State University, University of Missouri/Washington University, and Tufts University.

Integration of natural animal disease models, in the form of veterinary clinical trials, into disease research and treatment development is an innovative approach to improving translational efficiency. The goal of this project, and a necessary next step toward full integration of veterinary disease models into the translational pipeline, is the establishment of a SMART IACUC platform for single IACUC review of veterinary clinical trials. Successful completion of the work proposed in this application is vital to allow expeditious screening of promising new treatments in multi-site veterinary clinical trials designed to CONSORT standards and meeting all NIH guidelines for scientific rigor and transparent reporting. The three CTSA hubs involved in this application are uniquely positioned to complete the described projects because they are all actively collaborating on multi-site veterinary clinical trials with translational implications, have begun to move toward harmonized local processes in veterinary clinical trial review based on previous consultation with each other, and have partnered on previous CTSA-funded initiatives to develop foundational resources such as a veterinary-specific GCP training module, informed consent templates, and REDCap training programs for electronic data capture in veterinary clinical trials. The addition of Dr. Barbara Bierer as a collaborator from Harvard Catalyst further assures that the group can build upon existing CTSA resources and experiences developed as part of the SMART IRB initiative. The involvement of Drs. Sarah Moore and Cheryl London with the CTSA One Health Alliance (COHA) and its clinical studies subcommittee at the national level ensures broad dissemination of developed processes beyond the partner institutions associated with this proposal.

I am pleased to commit access to our local CTSA hub resources to contribute to the success of this project through our Translational Medicine comparative Animal Models Core, our Biomedical Informatics core and our Communications core for dissemination of the results as needed

Please do not hesitate to contact me with any questions you may have about this project.

Sincerely,

Personal Signature

Rebecca D. Jackson, MD
Max Morehouse Chair in Cancer Research
Director, OSU Center for Clinical and Translational Science
Principal Investigator, Clinical and Translational Science Award
Associate Dean for Clinical and Translational Research, OSU College of Medicine
Professor of Endocrinology, Diabetes and Metabolism, Department of Medicine

HARVARD CATALYST
Harvard Clinical & Translational Science Center

HARVARD UNIVERSITY

July 8, 2019

Sarah Moore, DVM, Diplomate ACVIM (Neurology)
Director, CCTS Comparative and Translational Medicine Program Associate Professor, Neurology and Neurosurgery
Co-director, Clinical and Translational Neurology Laboratory
College of Veterinary Medicine Department of Veterinary Clinical Sciences Veterinary Medical Center, 601 Vernon L. Tharp St. , Columbus , OH 43210

To the Scientific Review Committee,

As the Dean for Clinical and Translational Research at Harvard Medical School and Principal Investigator of Harvard Catalyst | The Harvard Clinical and Translational Science Center, I am writing to express my enthusiastic support for the project entitled “SMART IACUC: A path to harmonized veterinary multi-site trial review” submitted by the Ohio State University on behalf of themselves and the University of Missouri/Washington University, and Tufts University.

At Harvard, we have developed a national system of reliance for institutional review boards (IRBs) to which approximately 600 institutions have signed. We created a master reliance agreement that functions as a “treaty”- an agreement among the signatories- that outlines roles and responsibilities of the reviewing IRB and the relying institution, and a Joinder system to document institutional reliance. We developed robust resources and tools, webinars and checklists for education and operations. This effort evolved through support by NCATS into the SMART IRB system.

Our work is directly applicable to the SMART IACUC system proposed here, and operational efficiencies—without compromising animal protections—will help reduce time and administrative burden for translational research that often involves preclinical animal disease models. Barbara Bierer, MD, Director of Regulatory Policy, SMART IRB at Harvard will ensure that our knowledge, approach, and resources are shared and understood to help make this project a success.

Please contact me with any questions you may have.

Sincerely,

Personal Signature

Lee M. Nadler, M.D.
Virginia and D. K. Ludwig Professor of Medicine
Dean for Clinical and Translational Research
Harvard Medical School

The principal teaching hospital for Tufts University School of Medicine

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Harry P. Selker, MD, MSPH

Tufts Medical Center
Executive Director, Institute for Clinical Research and Health Policy Studies (ICRHPS)

Chief, Division of Clinical Care Research, Department of Medicine

Director, Center for Cardiovascular Health Services Research

Tufts University
Dean, Clinical and Translational Science Institute (CTSI)

Professor of Medicine

hselker@tuftsmedicalcenter.org

July 1, 2019

Dear Scientific Review Committee:

I am writing to express my support for the grant entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review," submitted in response to PAR-19-100: Exploratory CTSA Collaborative Innovation Awards R21. The purpose of this application is to develop a platform for rapid multi-institutional approval of clinical trials in veterinary patients to accelerated translational studies using naturally occurring models of disease. While the initial work will involve a collaboration among three institutions that are members of the CTSA One Health Alliance (COHA, Ohio State, Tufts, and the University of Missouri), the proposed platform will have substantial impact across all 15 academic centers that comprise COHA.

Over the past decade, the inclusion of veterinary patients into the translational paradigm has accelerated, with a multitude of ongoing studies exploring novel diagnostics and therapeutics for cancer, diabetes, cardiomyopathies, among others. This rapid growth has revealed a significant challenge associated with clinical trials involving veterinary patients. As there are currently no federal regulatory guidelines that specifically govern studies performed in client owned animals, oversight reverts to those established for research animals. In this setting, approval for trials involving pets is obtained through IACUC. However, the interpretation and application of guidelines for research animals to client owned animals varies widely across institutions, creating a substantial roadblock for efficient multi-center trial performance. As such, the overriding purpose of this project is to create a "SMART IACUC" platform for single IACUC review of trials that will enable expeditious initiation and completion. The platform will be designed to CONSORT standards and meet all NIH guidelines for scientific rigor and transparent reporting. The three CTSA hubs (Tufts, OSU, Missouri) have active cross-institutional trial collaborations, have partnered on previous CTSA funded initiatives, and are already working toward consensus with respect to trial approval and oversight. Dr. Barbara Bierer has been included as a collaborator from Harvard Catalyst to leverage existing CTSA resources developed as part of the SMART IRB initiative. Dr. Cheryl London will anchor the efforts at Tufts University, providing strong leadership with respect to comparative and translational medicine.

Tufts CTSI has been a leader in support of integrating a growing One Health Initiative and we very much look forward to continuing this effort.

Sincerely,

Personal Signature

Harry P. Selker, MD, MSPH

Washington University in St. Louis

Institute of Clinical and Translational Sciences

July 3, 2019

Dear Scientific Review Committee,

I serve as the PI of Washington University's Clinical and Translational Sciences Award. We have maintained strong collaborations with veterinary clinicians and scientists at the University of Missouri College of Veterinary Medicine. Thus, I am pleased to provide this letter of support for the project entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). This project is in complete alignment with this FOA as a highly innovative, exploratory collaborative research project developed by three institutions with outstanding NIH CTSA programs: The Ohio State University, University of Missouri/Washington University, and Tufts University.

We recognize the importance of comparative medicine and naturally occurring animal models of disease to advance translational and clinical research. As such, the University of Missouri College of Veterinary Medicine is a partner in our Institute of Clinical and Translational Sciences Consortium supported by our CTSA. A team of veterinary researchers have been identifying areas to streamline veterinary clinical trials across institutions to better serve the role of veterinary clinical trials in advancing medical knowledge. The goal of this project, and a necessary next step toward full integration of veterinary disease models into the translational pipeline, is the establishment of a SMART IACUC platform for single IACUC review of veterinary clinical trials. Completion of the work proposed here is essential to allow timely screening of promising new treatments in multi-site veterinary clinical trials designed to CONSORT standards and meeting all NIH guidelines for scientific rigor and transparent reporting. I am particularly excited about this proposal because the three CTSA centers involved in this endeavor are uniquely positioned to complete the projects described. Each of these institutions are currently collaborating on multi-site veterinary clinical trials with translational implications, and they are beginning to move toward harmonized local processes in veterinary clinical trial review based on previous consultation with each other. These programs have partnered on previous CTSA-funded initiatives to develop foundational resources such as a veterinary-specific GCP training module, informed consent templates, and REDCap training programs for electronic data capture in veterinary clinical trials. This group of veterinary clinician-scientists have shown their dedication to this SMART IACUC platform by seeking the advice of and including Dr. Barbara Bierer as a collaborator from Harvard Catalyst. This additional aid in building upon existing CTSA resources and experiences developed as part of the SMART IRB initiative. The involvement of Drs. Joan Coates and Angela McCleary-Wheeler with the CTSA One Health Alliance (COHA) and its clinical studies and biorepository subcommittees at the national level ensures broad dissemination of developed processes beyond the partner institutions associated with this proposal. Dr. McCleary-Wheeler additionally serves as a member of the COHA Steering Committee and can assist with communicating the results to COHA.

I am highly supportive of the concept of comparative medicine and the advances that can be achieved should we work to integrate this essential aspect of translational and clinical research. This proposal is well-positioned for success and will surely serve as a launching point for streamlining and improving collaboration to conduct strong veterinary clinical trials. As the PI of the Washington University CTSA, I assure that our CTSA will be supportive of

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Institute of Clinical and Translational Sciences

this work and help disseminate this work once it is completed. Please give this proposal your utmost consideration. Do not hesitate to contact me if you have any questions.

Sincerely,

Personal Signature

Bradley Evanoff, M.D., M.P.H.
Dr. Richard A. and Elizabeth Henby Setter Professor of Occupational, Industrial, and Environmental Medicine
Director, Institute of Clinical and Translational Sciences
Assistant Dean for Clinical and Translational Research
Chief, Division of General Medical Sciences
Professor of Medicine and Occupational Therapy

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Institute of Clinical and Translational Sciences

SCHOOL OF
VETERINARY MEDICINE
University of Wisconsin-Madison

July 2, 2019

Dear Dr. Moore,

I am writing in strong support for your proposed research project, entitled "SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted for an Exploratory CTSA Collaborative Innovation Award.

As a veterinary clinician scientist who is dedicated to promoting the involvement of veterinarians in translational research, I see a great need for a rigorous yet streamlined IACUC process for multi-institutional research in veterinary patients. This will pave the way for cost-effective and time-sensitive pre-clinical trials of drugs and devices that are promising for human use.

As the chair of Clinician Scientist Education for the CTSA One Health Alliance, I can attest that your proposed work also fills a substantial need in supporting veterinary faculty in balancing the conduct of clinical trials with other academic demands.

Successful completion of your project will result in the generation of an important resource that will improve the efficiency and impact of veterinary clinical trials for use as a translational research tool. I can commit to assisting your team with dissemination of resources associated with this project across the COHA network, by way of initiatives under our CTSA Innovation Award (U01TR002953). These include IACUC training in our Translational Research Immersion Program for early career veterinary faculty, and dissemination of best practices at our planned Translational Summits for MD and DVM researchers.

I sincerely hope that your initiative can come to fruition!

Sincerely,

Personal Signature

Lauren Trepanier DVM, PhD, DACVIM, DACVCP
Professor and Assistant Dean for Clinical and Translational Research
University of Wisconsin-Madison
School of Veterinary Medicine

NC STATE UNIVERSITY

Dr. Kathryn M. Meurs
Associate Dean for Research & Graduate Studies
919.513.6210
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College of Veterinary Medicine
1060 William Moore Dr.
Campus Box 8401
Raleigh, NC 27607

July 3, 2019

Dear Dr. Moore,

I am writing this letter to document my enthusiastic support for your proposed research project, entitled SMART IACUC: A path to harmonized veterinary multi-site trial review" submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). As the chair of the CTSA One Health Alliance Steering Committee, and Professor and Associate Dean for Research and Graduate Studies at North Carolina State University College of Veterinary Medicine, I am excited to see your project move forward from concept to a fully functioning national resource for veterinary multi-site clinical trials. As you know, my research focuses on comparative genomics and veterinary disease models. As such I am keenly aware of the challenges that come with site-specific review of clinical research. Your efforts toward a harmonized and singular process for review of multi-site veterinary clinical research promise to improve the veterinary clinical trial landscape across the COHA community and beyond by increasing rigor, efficiency, and ultimately translational scientific impact. I can commit to assisting your team with broad dissemination of resources and processes associated with the project across the COHA network of veterinary medical schools, and wish you success with this application.

Sincerely,

Personal Signature

Kate Meurs, DVM, PHD, DACVIM
Associate Dean for Research & Graduate Studies
College of Veterinary Medicine
NC State University

July 5, 2019

Dear Dr. Moore,

I am pleased to write this letter in support of your proposed research project, entitled “SMART IACUC: A Path to Harmonized Veterinary Multi-Site Trial Review,” submitted to funding opportunity announcement PAR-19-100 (Exploratory CTSA Collaborative Innovation Awards R21). As the chair of the CTSA One Health Alliance Communication and Collaboration Subcommittee and a veterinarian and Research Scientist at Colorado State University College of Veterinary Medicine and Biomedical Sciences, I believe that successful completion of your project can fill an urgent need in the veterinary clinical research community. More importantly, based on my own experience with clinical and translational research, I can attest to the importance of this project for improving the translational impact of veterinary clinical trials for disease research, therapeutic development, and ultimately improving human health. I am committed to using COHA Communication and Collaboration Subcommittee resources to assist your team with broad dissemination of resources and processes developed as outcomes of this project across the COHA network and beyond. I wish you success with this application.

Sincerely,

Personal Signature

Tracy L. Webb, DVM, PhD
Research Scientist II, Clinical Sciences
Clinical Review Board Coordinator, Research Integrity and Compliance Review Office
Colorado State University, Fort Collins, CO
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RESOURCE SHARING PLAN

Biologic Materials Sharing: There are no biological materials intended for use or generation as part of the proposed research plan.

Data Sharing: Data generated from this study will be published in peer-reviewed journals that are readily available worldwide and resources generated by the project will be made available across the COHA network via the COHA website. Additionally, resources will be shared via assistance of the COHA clinician-scientist subcommittee and communications subcommittee (see LOS from Trepanier and Webb, subcommittee chairs). Not all data generated by this research may be suitable for publication, but data will be provided to other academic investigators upon request, with the provision that use of these data by other investigators acknowledge the source of the data and that the data was obtained with support from the NIH.

Research Electronic Data Capture (REDCap) is available for use to all CTSA sites and affiliates. The REDCap platform at all participating centers will provide a fluid system for the study team to develop and execute cross-institutional reliance agreements, to conduct clinical trials, analyze data and share information in real-time. Surveys generated for the SMART IACUC platform will be available to other investigators of participating CTSA/COHA sites who have access to the program and can also be shared more widely upon request.

Material Transfers: The participating veterinary institutions will adhere to the NIH Grants Policy on Sharing of Unique Research Resources, including the “Sharing of Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts” issued in December 1999. http://grants.nih.gov/grants/intell-property_64FR72090.pdf While the proposed work is not expected to result in the use or generation of any biological materials, material transfers would be made in accordance with Material Transfer Agreement policies of the Ohio State University as relevant or required and which adhere to the NIH principles and policies on the sharing of biomedical research resources. Material transfers would be made with no more restrictive terms than in the Simple Letter Agreement (SLA) or the Uniform Biological Materials Transfer Agreement (UBMTA) and without reach-through requirements. Should any intellectual property arise from the NIH-funded research, which requires a patent, we would ensure that the technology remains widely available to the research community in accordance with the NIH Principles and Guidelines document.