

# History & Evolution of Post Approval Monitoring

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Lauren Cantamessa  
Assistant Director, Office of  
Research Compliance,  
IBC/IACUC Program Manager



1980's

1990's

2000's

2023

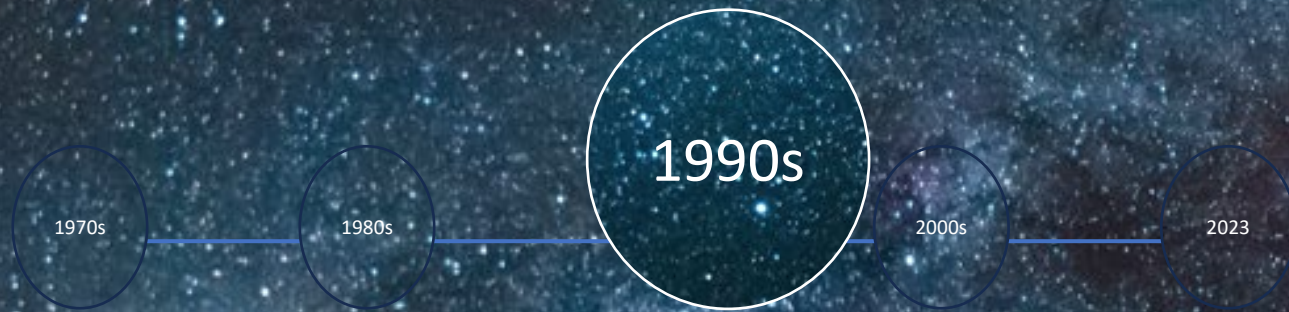
# Disclaimer

The opinions expressed are those of the presenters and may not necessarily reflect Montana State University.











1970s

1980s

1990s

2000s

2023



# Define Post Approval Monitoring



Post approval monitoring (PAM) is a program that monitors active projects to confirm that the research is being conducted as approved, thus ensuring compliance with the federal regulations, policies and guidelines that govern the protection of study participants.



Post-approval monitoring, also known as post-marketing surveillance or post-authorization safety surveillance, refers to the systematic and ongoing process of collecting and evaluating safety and effectiveness data for a product after it has been approved for marketing or authorized for use.

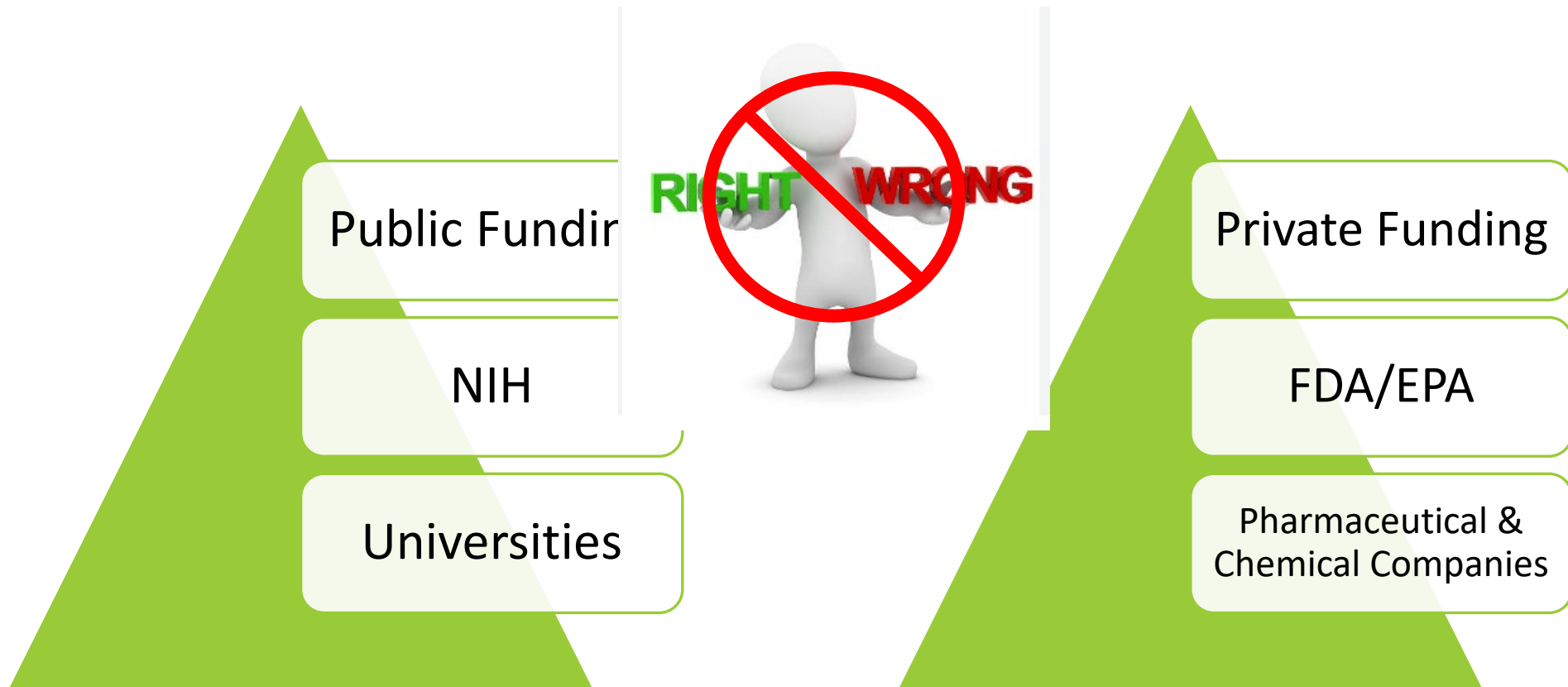


IACUC post-approval monitoring refers to the ongoing monitoring and oversight activities conducted by the Institutional Animal Care and Use Committee (IACUC) after a research protocol involving animals has been approved. The purpose of post-approval monitoring is to ensure that the approved protocol is being followed correctly, animal welfare is maintained, and compliance with regulatory requirements is upheld throughout the duration of the study.



# Biomedical Research in the 1970's

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# 1974

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- Tuskegee Syphilis Study
- Willowbrook Hepatitis Study
- Fernald State School Trials

# 1974

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- Industrial Biotest Laboratories
- G.D. Searle & Company



1974

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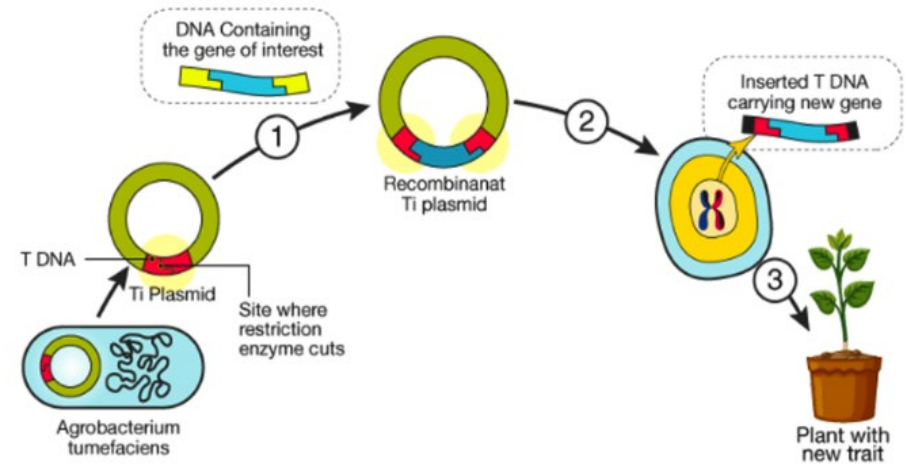
# IRB

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# 1976

## rDNA



- 1 Treat foreign DNA and plasmid with restriction enzyme and DNA ligase.
- 2 Introduce the recombinant plasmid into cultured plant cells.
- 3 Regenerate new plant from cultured cells.

IBC

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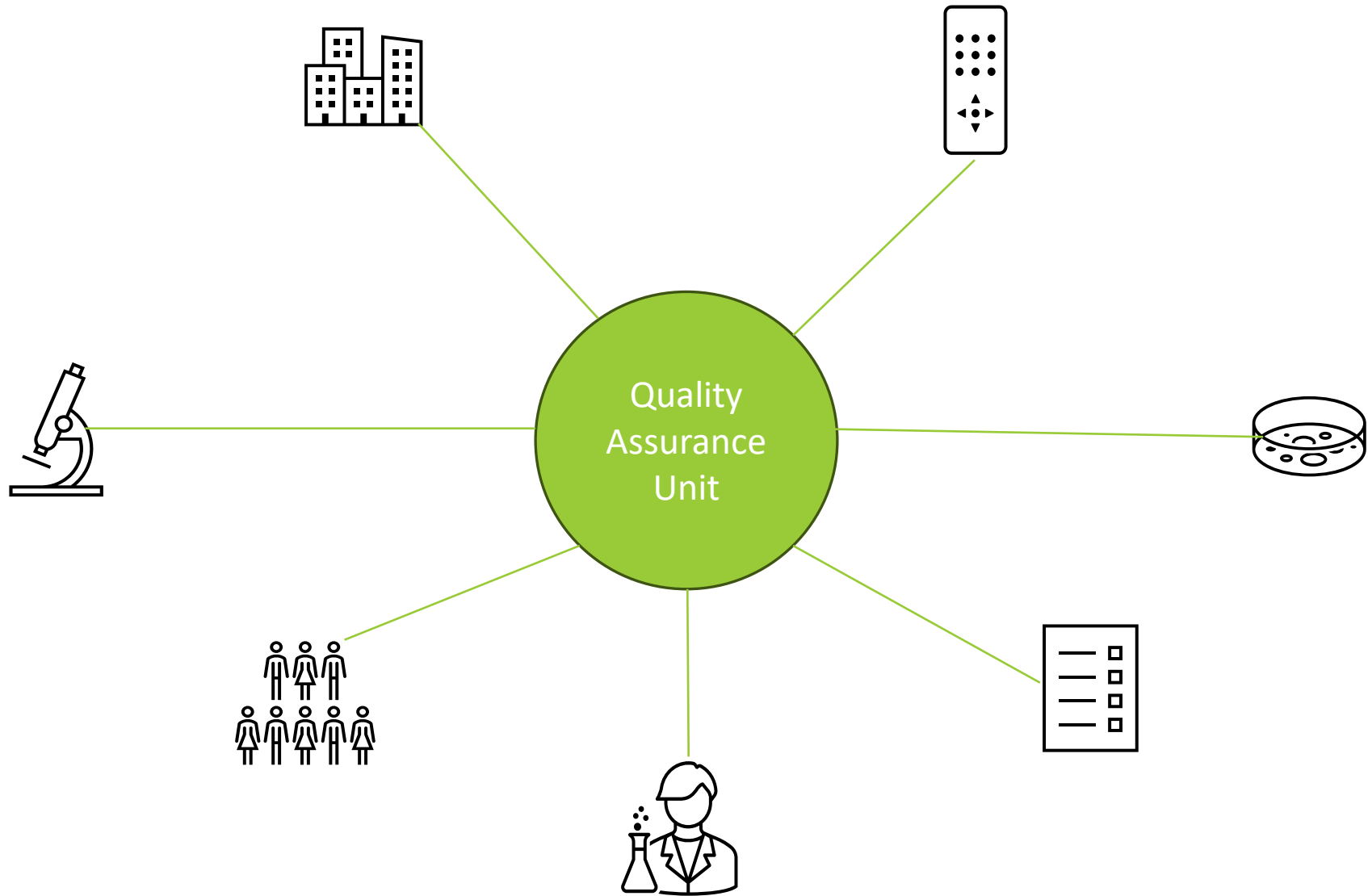
1979



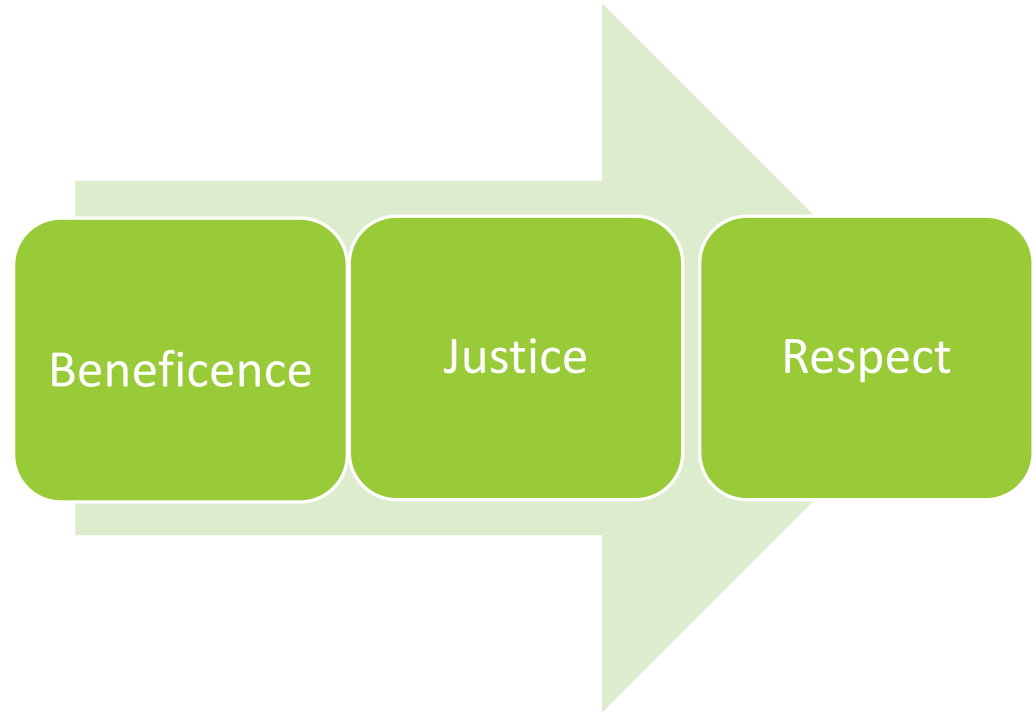
## § 58.35 Quality assurance unit.

- (a) A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study.

Quality  
Assurance  
unit



1979





**ANIMALS ARE NOT OURS**

to experiment on, eat, wear, use for entertainment, or abuse in any other way. ▶▶



**Become a Member**

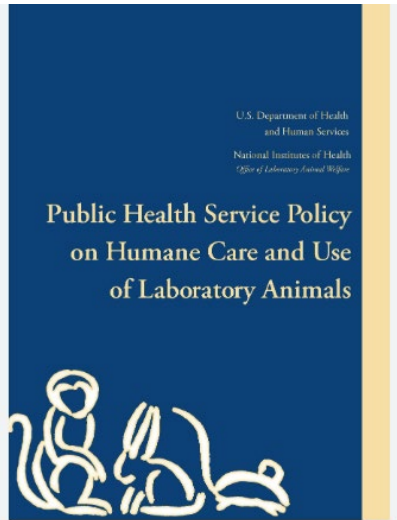
**Renew Your Membership**

**GET PETA UPDATES**

E-Mail Address



**THE HUMANE SOCIETY OF THE UNITED STATES**



1985/86

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IACUC

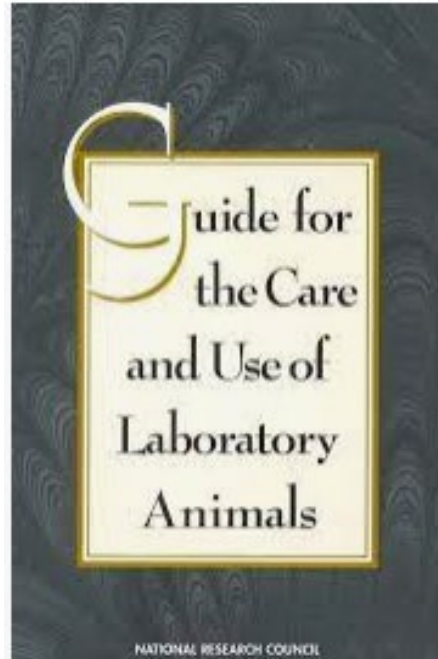




**PRIM&R**  
PUBLIC RESPONSIBILITY IN  
MEDICINE AND RESEARCH



Association for the Accreditation  
of Human Research Protection Programs, Inc.



# 2011

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“PAM is considered here in the broadest sense, consisting of all types of protocol monitoring after the IACUC’s initial protocol approval.”




IBC

IIACUC

Research  
Compliance

IRB



A person is walking away from the viewer down a long, brightly lit tunnel. The tunnel's walls are covered in a large, glowing clock face with Roman numerals. The background is a vibrant, colorful space scene with stars, nebulae, and streaks of light. A thought bubble is positioned in the upper right corner of the image.

Next to doing the right thing,  
the most important thing is to  
let people know your're doing  
the right thing. J.D Rockefeller

# Post Approval Monitoring:

*Are we doing what we said  
we'd do?*

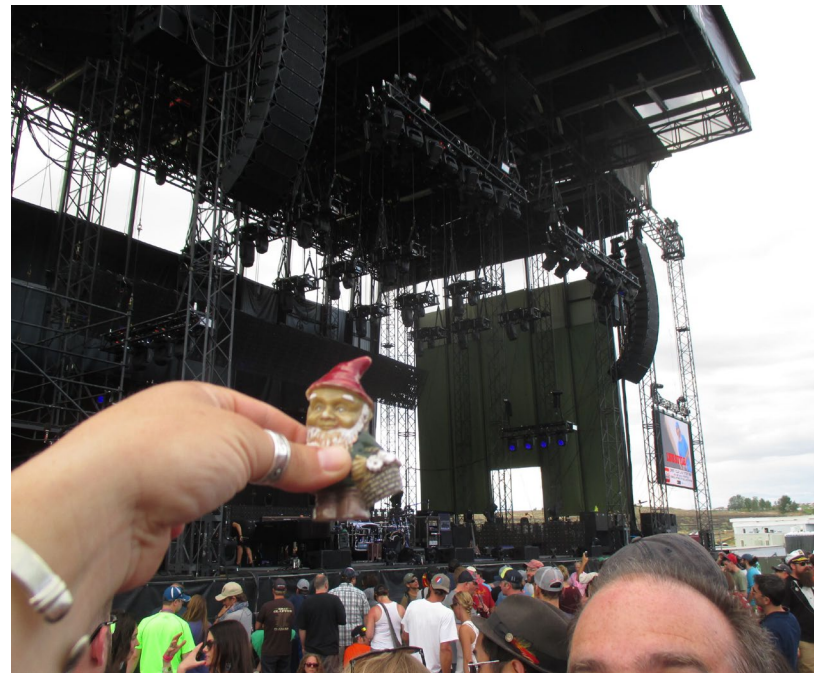
*Amy Robison – Interim Biosafety Officer*



# Disclaimer

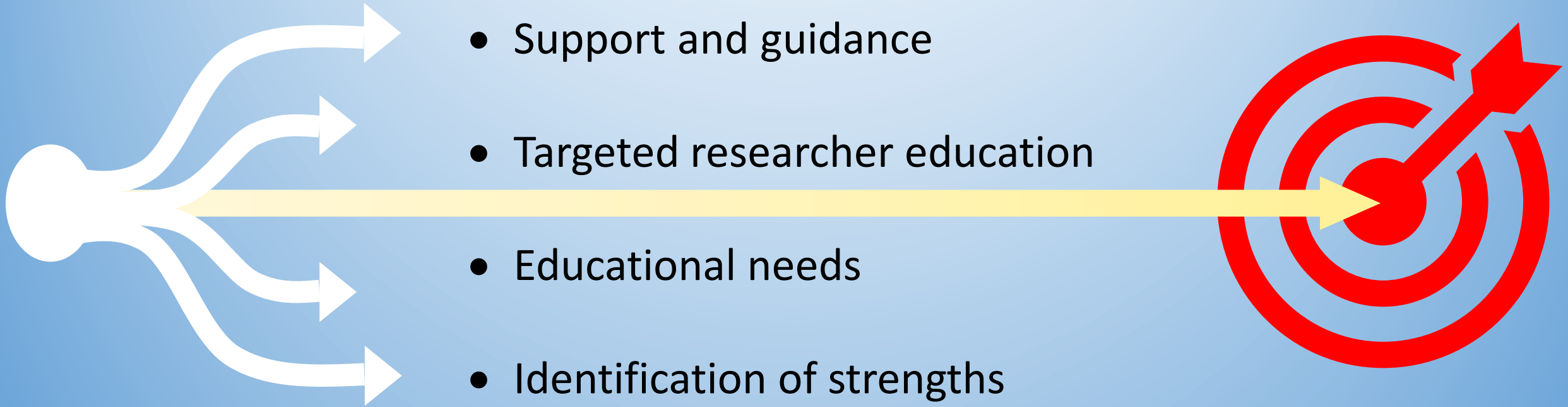
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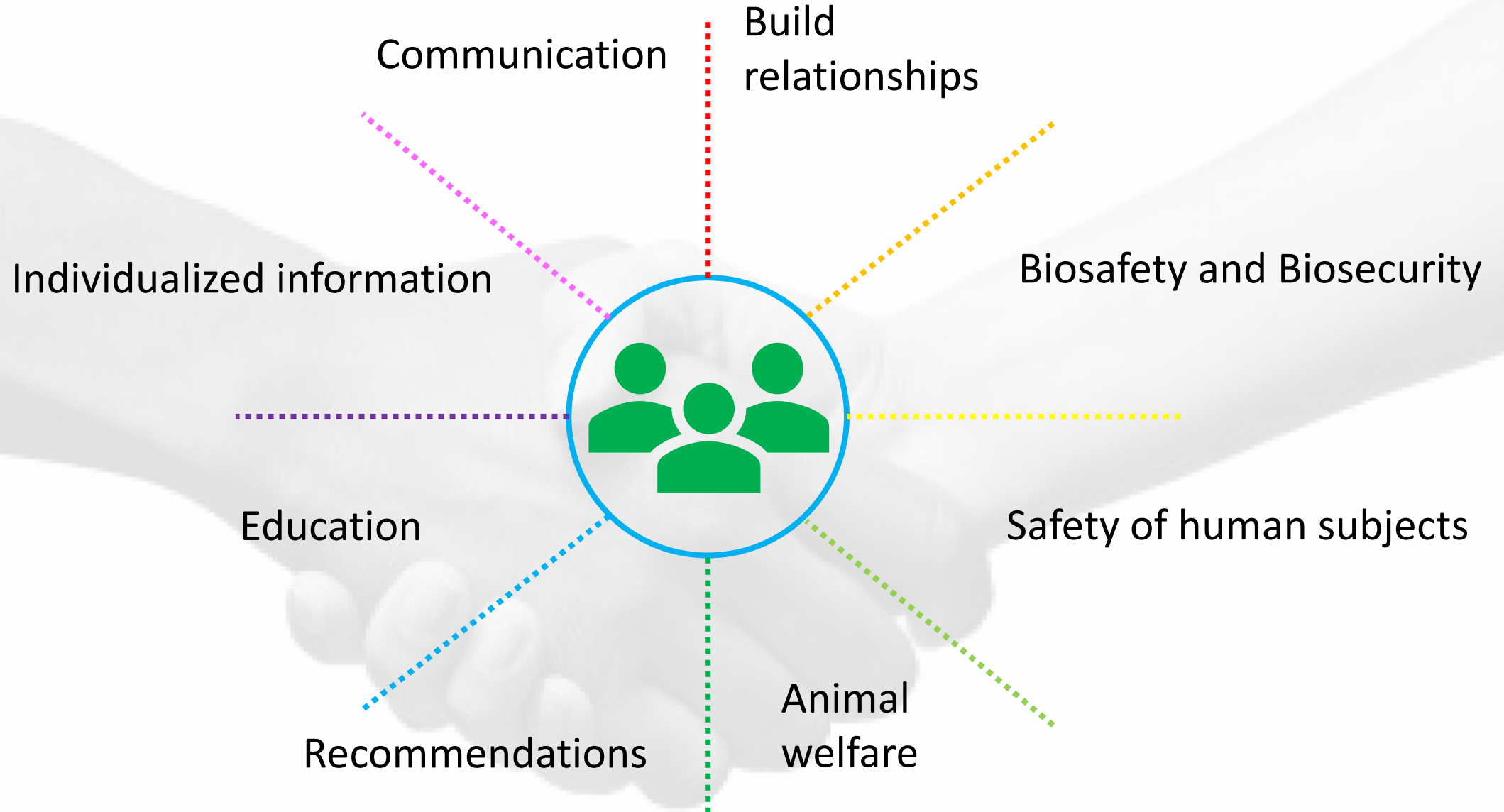


# PAM Objectives

- Internal process
- Support and guidance
- Targeted researcher education
- Educational needs
- Identification of strengths
- Preparation for external audits



# Benefits of PAM



# What the PAM is not?!

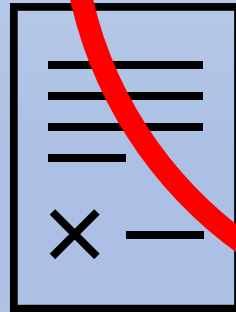
New ground or a new regulation



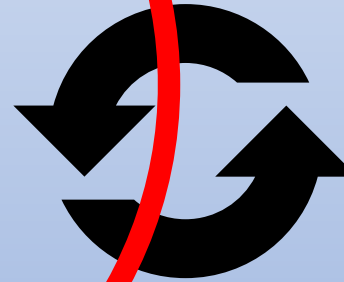
Research police



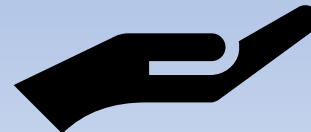
Required by sponsors or federal agencies (USDA, PHS, CDC, APHIS, etc.)



Replacement for the committee



A funded mandate





assistant liaison guide network  
colleague monitor team member community relationship  
collaborator ally associate  
cmony comrade officer  
connection comrade cooperation  
partner

# Visiting Labs



- Prepare
- Engage
- Show interest
- Observe
- Attitude is Everything!

# Attitude

is

# Everything!

Perfection

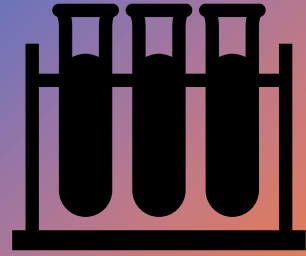
Drift

Adverse  
Events

Research  
Staff

Campus  
Stewards

# Continue the loop



- POST-ASSESSMENT Follow up
- Terminology is everything!
- Culture of Compliance  $\neq$  Compliance police



# Is your PAM working?



Amendment requests

Self-assessment

Protocol submission  
quality goes UP!

Tracking adverse events

Increased research  
community  
relationships

Select Approved Protocol	
Drag a column header and drop it here	
<input type="checkbox"/>	Protocol #
<input type="checkbox"/>	2022-97-IBC
<input type="checkbox"/>	2023-64-IBC
<input type="checkbox"/>	2022-399-IBC
<input type="checkbox"/>	2021-62-IBC
<input type="checkbox"/>	2023-468-IBC
<input type="checkbox"/>	2021-75-IBC
<input type="checkbox"/>	2022-105-IBC
<input type="checkbox"/>	2021-77-IBC
<input type="checkbox"/>	2023-466-IBC
<input type="checkbox"/>	2022-106-IBC
<input type="checkbox"/>	2022-36-IBC
Total Records: 100	

Select Approved Protocol	
Drag a column header and drop it here	
<input type="checkbox"/>	Protocol #
<input type="checkbox"/>	2022-109-IA
<input type="checkbox"/>	2022-215-IA
<input type="checkbox"/>	2022-158-IA
<input type="checkbox"/>	2022-202-IA
<input type="checkbox"/>	2023-311-IA
<input type="checkbox"/>	2021-176-IA
<input type="checkbox"/>	2022-94-IA
<input type="checkbox"/>	2023-238-IA
<input type="checkbox"/>	2023-65-IA
<input type="checkbox"/>	2022-190-IA
<input type="checkbox"/>	2022-213-IA
Total Records: 71	



Hello Dr. **xxx**,

Your IACUC protocol **xxx** has been selected to be reviewed through the IACUC's Post Approval Monitoring (PAM) process. This monitoring is simply one method whereby the IACUC, through the conduct of periodic reviews of programs and procedures, ensures that animal studies are being performed in compliance with approved protocols as dictated by the federal Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*.

IACUC representative(s) would like to meet with you and key members of your staff to discuss your protocol, review records and monitor animal procedures associated with the protocol.

Could you please supply us with a few days and times within the next three weeks that are amenable to such meetings and/or monitoring? We would like to meet in a conference room or office initially, and then observe some animal procedures. Thank you for your cooperation and support to help strengthen MSU's animal programs.

Attached is the PAM Checklist we will use for reviewing your protocol.

Regards,

	Sun	Mon	Tue	Wed	Thu	Fri	Sat
	15	16	17	18	19	20	21
				Free			
8 AM		Tentative	Busy	Tentative	Busy	Tentative	
		Busy	Busy		Busy		
9 AM		Busy	Busy		Busy		
		Busy					
10 AM			Busy	Busy		Busy	
		Busy				Busy	Tentative
11 AM		Busy					
12 PM						Tentative	
1 PM							
2 PM					Busy		
3 PM			Busy				
			Busy	Busy			
4 PM				Busy			
5 PM							





IRB numbers: NJ-H041618  
NJ-H020818

*closed*  
*closed this summer*  
*no blood from either protocol.*

A growing body of research documents a relationship between our socioeconomic exposures and physical health across the lifespan. More specifically, evidence suggests that early life family environments characterized by conflict or abuse, and socioeconomic adversity increase risk for ill health in adulthood, while positive qualities in the early family environment may protect from the negative health consequences associated with these exposures (John-Henderson, Rheinschmidt, Mendoza-Denton, Francis, 2015; John-Henderson, Marsland, Kamarck, Muldoon, Manuck, 2015; John-Henderson, Kamarck, Muldoon, Manuck, 2015; Chen, Miller, Kobor, Cole, 2011). Retrospective studies indicate that early life family conflict shapes social interactions in adulthood (John-Henderson et al., 2015). However, little is known about how early life familial and socioeconomic exposures interact to inform important health behaviors, social interactions, and access to social support among college students.

In this study, we will utilize ecological momentary assessment which will allow for the measurement of the nature and frequency of stress exposure and social interactions, ambulatory blood pressure, and health behaviors (e.g., sleep, diet) as they unfold in real time on the participant's own smartphone. This design offers an important advantage compared to in-lab assessments of these measures as they avoid recollection errors or bias, and provide a dynamic picture of how these measures may change over the course of the day and from day to day, and further how differences in socioeconomic status may affect these factors in the individual's environment on a daily basis. Specifically, participants will be asked about their current mood, recent social interactions, dietary intake, and perceived stress.

In addition, we will collect salivary and dried blood spot samples to assess levels of biomarkers associated with disease risk. Specifically, we will measure systemic levels of immune system inflammatory markers (e.g., interleukin-6) in dried blood spot samples. Elevated levels of IL-6 associate with increased risk for numerous diseases including cardiovascular disease. In addition we will use salivary samples to measure circulating levels of cortisol. This research design will allow us to consider the relationship between a physiological measure over the course of the day (ambulatory blood pressure), daily social, psychological and behavioral factors with a known marker of disease risk.

We will utilize enzyme linked immunosorbent assays to measure levels of salivary cortisol and levels of inflammation from dried blood spot samples. For the blood spot samples we will follow the protocol developed by McDade (2012) for a highly sensitive immunoassay for interleukin-6 in dried blood spot samples. To summarize, we will use a HTS filter plate and elute two 5 mm hole punches from the dried blood spot samples in 100 microliters of PBS in each well. The plate will be covered with a plate cover and will incubate at 4C overnight on top of a NUNC 96 well plate. The next morning, the HTS plate will be stacked on top of an R&D HS IL-6 ELISA plate and centrifuged for 10 minutes at 2000 rpm. The plate will incubate with shaking at 500 rpm at room temperature for 2 hours. The plate will then be washed 6 times with the wash buffer provided in the ELISA kit after which 200 microliters of conjugate will be added. The plate incubates for another 2 hours and then is washed again 6 times. Then 50 microliters of substrate is added to each well and the plate incubates for 60 minutes. Then 50 microliters of amplifier solution is added to each well and the plate incubates for 30 minutes. Finally, 50 microliters of stop solution is added and the plate will be read at 450 nm within 30 minutes.

Salivary samples will be spun down in the centrifuge and then analyzed using the Salimetrics cortisol ELISA.

Sample collection and handling: Dried blood spots are collected in 414 Traphagen hall using a single-use finger lancet. Each participant will place 5 spots of blood from the finger on a protein saver card. This card is placed in a specimen ziploc bag and stored in a -20 Freezer in Leon Johnson Hall. Saliva samples are collected using the Sarstedt Collection device.

Participants place the swab in their mouth for 60 seconds and then place it back in the collection device. Samples are then stored in a -80 freezer in 523 Leon Johnson Hall. Dried blood spots samples will be eluted when ready for ELISA analysis (using the procedure outlined previously) and saliva samples will be spun down in a centrifuge in 523 Leon Johnson before analysis for cortisol levels using the salimetrics ELISA.

All unused samples will be autoclaved and disposed of in accordance with BSL2 protocol for sample disposal.

Confidentiality Statement

Page 5 of 18

*if collecting, need to have an active IRB*  
*old samples*  
*yes identifiers, need IRB*  
*no identifiers, don't need IRB*

*Freezer inventory?*

This form is used for Post-Approval Monitoring (PAM) by the Office of Research Compliance of all laboratories that have a current IBC protocol at Montana State University. MSU has made a commitment to maintain a program in accordance with the current edition of the Biosafety in Microbiological and Biomedical Laboratories, the NIH Guidelines, USDA/APHIS permitting requirements, OSHA Bloodborne Pathogens Standard, and all MSU biosafety policies.

Questions/Concerns/Comments: Please call MSU Biosafety Officer Ryan Bartlett Phone: 406-994-6733 E-mail: ryan.bartlett@montana.edu

References: Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules MSU Biosafety Manual

1.0 Protocol Information

1.1 Are all personnel performing work on the protocol are listed? (If human-derived materials are used, all staff who are present during work are listed.) *training?*

1.2 All IBC related records (CITI or in-person training, risk assessment, etc.) are retained in an accessible location for study personnel.

1.3 Are all building and room numbers where work with biological agents listed on the protocol? *Traphagen 414?*

1.4 Is the protocol associated with any other protocols (IACUC, IRB, IBC, RAD)? *yes IRB but not accurate work on updating.*

1.4.1 Are associated protocols listed in TOPAZ? *no*

1.5 If there were any changes (personnel, procedures, etc.) to the approved protocol since the last review, was an amendment submitted to the IBC? *amendment 9/2/22 -> amend personnel.*

1.6 Has the study been audited by a funding or other agency (NIH, NSF, CDC, USDA)? *no*

1.6.1 Is there documentation? *N/A*

1.6.2 Have any corrective actions been completed? *N/A*

*yes Admin*  
*add.*  
*yes*  
*414?*  
*yes*  
*accurate*  
*work on*  
*updating.*

2.0 Biological Agent Information

2.1 Are all biological agents being used listed on the protocol with accurate Genus, species, and strain?

2.2 Are the biological agents being worked with at the appropriate physical containment level (i.e., biosafety level)? *where are the saliva & blood samples pipetted? ok.*

2.3 Are all relevant pathogen safety data sheets (PSDS) available for lab staff? *on bench top.*

2.4 Are any biological toxins listed on the protocol?

2.4.1 Are the amounts possessed within limits?

2.5 Is any work with recombinant or synthetic nucleic acid molecules performed for this protocol?

2.5.1 Are all hosts, vectors, and genes of interest listed?

2.5.2 Are all relevant NIH Guidelines being followed?

*n/a*  
*says BSL2*  
*but no*  
*n/a use*  
*of*  
*BSE.*

*no*  
*n/a*

3.0 Biological Material Storage Information

3.1 An accurate inventory of biological materials is available. *good, on doors of freezers*

3.2 Containers are labeled in accordance with MSU requirements. *comple stickers*

3.3 If required, biological materials are stored in a locked location.



# Prepare

Mountains & Minds



Institutional Animal Care and Use Committee  
 Office of Research Compliance  
 P.O. Box 173085  
 Bozeman, MT 59717

**Post Approval Monitoring Checklist**

IACUC Protocol#: \_\_\_\_\_ Date: \_\_\_\_\_

Person/s performing PAM: \_\_\_\_\_

Other associated protocols (e.g., IBC): \_\_\_\_\_

*This form is used for Post-Approval Monitoring (PAM) by IACUC members of all laboratories that conduct any animal research, research training, experimentation, biological testing, or related activities involving live vertebrate animals at Montana State University. As an OLAW-assured institution, MSU has made a commitment to maintain a program in accordance with the current edition of the "Guide for the Care and Use of Laboratory Animals".*

*Instructions: Complete this form manually while performing PAM inspection of PI's protocol. NOTE that CTI stands for "corrected at time of inspection".*

Protocol and Personnel	Yes	No	NA	CTI	Comments
The PI and all project personnel have access to the most recent version of the protocol					
Modifications have been submitted for any changes to the protocol, including personnel					
All personnel working on the project are listed on the protocol and have completed ARC and CITI Training					
All personnel on this protocol have reviewed the protocol with the PI or other senior personnel					
Each building and room number where animals are taken outside of the ARC are listed on the protocol					
Additional notes:					
General Procedures	Yes	No	NA	CTI	Comments
Procedures used are the same as those described in the protocol					
Species and numbers of animals are consistent with those in the protocol					
All drugs, fluids, sutures, gloves, and other materials are within expiration dates; no expired items are present					
Only pharmaceutical-grade compounds are used unless otherwise approved in the protocol					



Office of Research Compliance  
 Institutional Review Board  
 123 Hamilton Hall 406-994-4706

**Post Approval Monitoring Checklist**

IRB#: \_\_\_\_\_ PI: \_\_\_\_\_ Date: \_\_\_\_\_

Project title: \_\_\_\_\_

Person/s performing PAM: \_\_\_\_\_

Related protocols (i.e., IBC): \_\_\_\_\_

Approval and Record Keeping	Yes	No	NA	CTI	Comments
The project has current IRB approval.					
Are all personnel listed on the protocol?					
Have protocol personnel completed training - including a base human subjects research course, study-specific, etc.? Is there documentation?					
All IRB related records (approval letters, protocol form, consent forms, recruitment material, correspondence, etc.) are retained in an accessible location for protocol personnel.					
Are there procedures in place to retain records for 3 years after the research is complete? Show current storage for existing subject records.					
Consents	Yes	No	NA	CTI	Comments
Are the enrollment numbers less than or equal to the number approved by the IRB in experimental (research) and control (normal) groups?					
Does the consent process match the latest IRB approved procedure?					
Do the subjects receive a signed copy of the consent form or at a minimum offered the opportunity to do so?					



# Interview/Observe

Mountains & Minds

To: Dr. [REDACTED]

Subject: Post Approval Monitoring: IBC Protocol 2020-[REDACTED]-IBC

Dear Dr. [REDACTED],

The IBC has completed a Post Approval Monitoring (PAM) of protocol 2020-[REDACTED]-IBC, "[REDACTED]". The results were reviewed and discussed during the [REDACTED] 2023 IBC meeting.

**Summary:**

On February [REDACTED], 2023, the IBC conducted a PAM of protocol 2020-[REDACTED]-IBC. Items that were reviewed included:

- Consistency of protocol with work being performed
- Freezer inventory
- Personnel
- Waste disposal
- Training records

Members of the Office of Research Compliance met in Leon Johnson [REDACTED] with key staff listed on IBC Protocol 2020-[REDACTED]-IBC. Individuals present for the PAM:

- Ryan Bartlett, Biosafety Officer
- Amy Robison, Laboratory Safety Specialist
- [REDACTED], Lab Manager

During the meeting, Ryan and Amy performed the PAM utilizing the checklist that was provided to staff prior to [REDACTED].

Thanks to you and your staff for assisting with this monitoring program. The lab specific binder, SOPs and spill kit are easy to locate for your staff. The PPE in the lab is in good condition and congruent with what is listed in the protocol.

**Findings:**

1. Protocol Section 2.7, Building Locations: The narrative states that blood is collected onto protein saver cards occurs in Traphagen [REDACTED]. [REDACTED] verified this during the PAM.

**Corrective action:** Submit an amendment to add the Traphagen location to the protocol.

2. Protocol Section 2.9, Protocol Objectives: Includes closed IRB protocols.

**Corrective action:** Submit an amendment to remove the closed listed IRB protocols.

3. Protocol Section 2.10, Related Research Protocols:

- a. During the PAM pre-review, Amy could not identify any IRB protocols that are approved for blood collection via lancet onto a protein saver card. [REDACTED] remarked during the PAM that she would have the lab update an IRB protocol to include this procedure.
- b. The IRB protocol listed (2020-[REDACTED]) is not associated with the research described in Section 2.9.

- a. Submit an amendment to an IRB protocol. After approval, submit an amendment to the IBC protocol to include the IRB protocol as a related protocol.
- b. Submit an amendment to remove IRB Protocol 2020-[REDACTED].

4. Protocol Section 3.1, Protocol Associates:

- a. During the PAM, [REDACTED] mentioned that two people listed are no longer in the lab.
- b. Staff Competency: [REDACTED] is missing Bloodborne Pathogens Training.

**Corrective action:**

- a. Submit an amendment to remove: [REDACTED] and [REDACTED].
- b. Have [REDACTED] complete BBP training.

5. Protocol Section 11.20: Date of Lab Self-Inspection is out of date.

**Corrective action:** Submit an amendment with the updated date.

6. Protocol Section 11.21: Transportation and Shipment of Biological Agents: Since the narrative Section 2.9 states that blood is collected in Traphagen and stored in Leon Johnson, transportation between buildings on MSU campus is applicable.

**Corrective action:** Submit an amendment to check the box for "transporting biological agents between laboratories or buildings on MSU campus".

**Actions for ORC to do:**

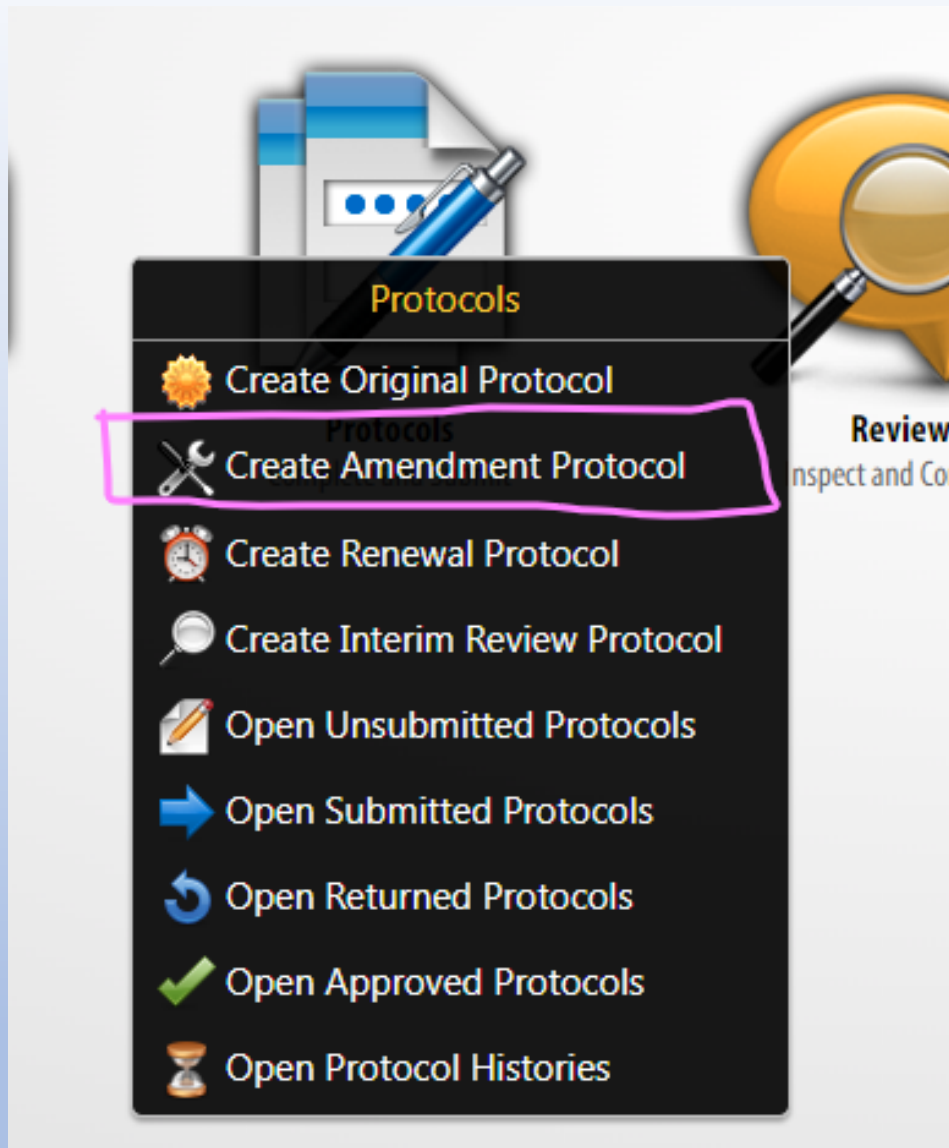
1. We will bring some biohazard stickers to the lab to apply to new equipment.
2. We will email [REDACTED] the template for Emergency Contacts from the Biosafety website to update the lab specific manual.

Thank you,

Ryan Bartlett, MS, RBP  
Biosafety Officer

Amy Robison  
Laboratory Safety Specialist

<u>Date of PAM</u>	<u>Protocol</u>	<u>PI</u>	<u>Finding</u>	<u>CAP</u>	<u>Completion date</u>
2/10/2023	2020-██-IBC	██████████	1. Protocol Section 2.9, Protocol Objectives: a. Includes closed IRB protocols. B. The narrative states that blood is collected on protein saver cards in Traphagen 414. In follow up with the Principal Investigator, it was stated that blood spots are no longer being collected as part of this research project.	a. Submit an amendment to remove the closed IRB protocols. B. PI must provide written confirmation that blood spots are no longer being collected, and clarification if blood spot cards are being stored and utilized for research. Submit an amendment to remove the collection of blood samples.	5/9/2023
			2. Protocol Section 2.10, Related Research Protocols: The IRB protocol listed (2020-76-JC080420-FCR) is not associated with the research described in Section 2.9.	Submit an amendment to remove IRB Protocol 2020-76-JC080420-FCR. Ensure the accurate, approved IRB is included in Related Research Protocols.	5/9/2023
			3. Protocol Section 3.1, Protocol Associates: a. During the PAM, ██████ mentioned two people listed are no longer in the lab. B. Staff competency: ██████ is missing Bloodborne Pathogens Training.	a. Submit an amendment to remove: ██████ and ██████. B. Have ██████ complete BBP training.	5/9/2023



<u>Completion date</u>	<u>Action/change</u>	indicates completed
5/9/2023	checked 5/5/23: a. not done, b. not done.	7 day email notification sent 5/9/23
5/9/2023	checked 5/5/23: not done	
5/9/2023	checked 5/5/23: a. not done, b. not done.	

# Conclusion



Thank you!

Amy Robison – Interim Biosafety Officer

[amanda.robison@montana.edu](mailto:amanda.robison@montana.edu)

406-994-6733