Webinar 1: Streamlining Institutional Requirements for Animal Research

Ara Tahmassian (AT) – Institutions Response
Sally Thompson-Iritani (STI) – Institutions Response
Axel Wolff (AW) – NIH OLAW Response
Betty Goldentyer (BG) – USDA Response
Molly Greene (MG) – IACUC/Investigator Response
J.R. Haywood (JRH) – IACUC/Investigator Response
Gaylen Edwards (GE) – IACUC Investigator Response

Questions:

***** For PHS/NSF supported studies, the OLAW answer supersedes the others.

1) Animal numbers if approximate, then can approximate numbers be submitted as part of the USDA Annual report?

BG: Animal numbers submitted on the USDA Annual Report should be correct. You may submit numbers gathered prospectively as long as any changes to a higher pain category are reflected.

Institutions: The USDA annual report is retrospective so should have accurate numbers.

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2) Can the team speak to whether there is a regulatory requirement to account for individual strains (e.g., transgenics, cross strains, etc.) in the protocol? What about breeding protocols?

BG: Under the AWA, accounting for individual strains would be a decision for the IACUC, including breeding protocols.

Institutions: With the complex nature of genetically modified crosses we do not require each individual strain be listed. Any strain that is associated with abnormal phenotypes or special monitoring requirements should be listed.

AW: The Guide states that genetic characteristics are important with regard to the selection and management of animals for use in breeding colonies and in biomedical research (pp. 76-77). The determination as to whether to include a strain in the protocol is left to the discretion of the IACUC to most appropriately meet institutional needs. Therefore the IACUC may decide which strains are to be included, especially if known phenotypic complications may result. A description of any clinical conditions that require special support or known morbidities that require intervention to minimize pain and distress should be included. This applies to breeding protocols as well. Changes in strain within an approved protocol do not require IACUC review or approval.

3) Regarding animal numbers, could Dr. Wolff please comment on the "should" statement in the Guide that indicates the need for statistical justification for group size as it relates to permitting a range of animal numbers?

AW: The *Guide* (p.8) states that *should* indicates a strong recommendation for achieving a goal; however individual circumstances might justify an alternative strategy. As such the statement that the number of animals and experimental group sizes should be statistically justified (whenever possible) can be achieved by using an estimate. If the PI estimates that the study can be accomplished with approximately 200 mice, then identify this number in the Vertebrate Animal Section in the grant application, the protocol, and in the statistical analysis. If this number is later found to be inadequate or too high, the protocol can be amended by the methods described in the presentation. For individual cohorts, a range can be used such as 10-15 animals in each experimental group.

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4) Depending on applicable regulations, documentation is required to be maintained for 3 years beyond the completion of protocol activities. If a protocol is not rewritten at triennial review and is therefore a continuing activity, then it could be interpreted that there is no completion date applicable. In that case, is there guidance on when 'historic' documentation can be discarded?

BG: Under the AWA, records that relate to proposed activities shall be maintained for the duration of the activity and an additional 3 years. In this case, since the protocol was not rewritten and is considered a continuing activity, 'historical' documentation should be retained and the '3 year retention beyond the completion' starts when the activity is no longer continuing.

Institutions: The protocol is re-reviewed every 3 years in its entirety so this is a restart of the protocol in our system. For longer lived species it is important to remember that records need to be maintained for the life of the animal.

AW: The PHS Policy (IV.E.2) states that "all records shall be maintained for at least three years; records that relate directly to applications, proposals, and proposed significant changes shall be maintained for the duration of the activity and for an additional three years after completion of the activity." When the protocol in question is terminated, all records associated with it shall be maintained for three years. Only the most recent version of the protocol needs to be maintained for three years after the project has ended.

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5) The Guide states that "whenever possible, the number of animals and experimental group sizes should be statistically justified." (page 25)

Institutions: Agreed. Whenever possible it is important to statistically justify animal numbers. It is also important to remember that statistics is only as good as the data used to generate the power analysis so there may be times when ranges and approximations make sense if there is limited data to base the statistical analysis on.

AW: See #3

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6) *Can COGR please reach out to the DOD regarding its regulations??*

Institutions: There was participation at the PRIMR Conference this year from DOD ; have heard that there was great discussion.

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7) Regarding the administrative review, are there any requirements or suggestions on who can conduct such a review and if an official approval letter or notification to the PI is necessary?

BG: The IACUC can determine the best process for the continuing review and who can conduct it. There is no requirement for an official approval letter.

Institutions: Items that can be approved administratively should be done in accordance with the guidance of the IACUC and anyone should be able to do this. We do not produce an approval letter.

AW: Administrative changes can be handled by an IACUC coordinator or IACUC staff and do not require IACUC approved policies, consultations, or notifications. In situations where qualified staff (other than PI) is added to the protocol, the protocol should be updated. (See also #22 https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html and https://olaw.nih.gov/guidance/significant-changes.htm)

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8) Regarding animal numbers, what about the methods of counting young animals such as mouse pups?

*AW: Rodent pups are to be accounted for at the first manipulation (cage change, genotyping). Approximate numbers are to be recorded at that time. This accounting should not be delayed to a later time point such as weaning. Although the PHS Policy does not explicitly require a mechanism to track animal usage by investigators, it does require that proposals specify a rationale for the approximate number of animals to be used and be limited to the appropriate number necessary to obtain valid results. This implicitly requires that institutions establish mechanisms to document and monitor numbers of animals acquired and used, including any animals that are euthanized because they are not needed. Monitoring should not exclude the disposition of animals inadvertently or necessarily produced in excess of the number needed or which do not meet criteria (e.g., genetic) established for the specific study proposal. (Also see #41 and https://olaw.nih.gov/guidance/faqs#660)

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9) Do you feel that a 10% increase in animal numbers is appropriate when it comes to the animal range requirement? I think this question has to do with the range of animals being used, too.

Institutions: This should be at the discretion of the IACUC and maybe dependent on species and study design. Many IACUCs are comfortable with a 10% variance.

AW: That is for the IACUC to decide when developing policies for significant changes to address increases in animal numbers. IACUCs are welcome to use a percentage, an exact animal number, a relative number, or allow no deviation. Policies that specify the acceptable range for animals used must have documentation as the numbers change. Those changes may need to be supported by a revision of the rationale for number of animals used and this also must be documented.

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10) If a range is allowed, but a statistical analysis SHOULD be use, how can a range be appropriate.

Institutions: see #5 above.

AW: See #3 The PI is to determine which estimate within the range is the best fit for the statistical application.

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11) Is a DOD/ACURO representative involved in the 21 CCA working group?

BG: DOD is not a member of the 21 CCA working group. The working group consists of NIH, USDA and FDA.

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12) On the topic of approximation of animal numbers, should the IACUC still request a maximum number of animals to be used?

MG: There is no requirement for the PI to state nor the IACUC to request a maximum number of animals to be used.

Institutions: The PI should request the number of animals that they need.

*AW: Yes, the approximate total number of animals by species is to be listed in the protocol. The total number may be provided as a range.

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13) I realize USDA does not require lit search for category C. Does PHS require this? Also does PHS require lit search for non-regulated species?

MG: The PHS Policy does not require a lit search but does expect PIs to consider and IACUCs to review consideration of alternatives and the 3Rs.

Institutions: Agree with explanation above (e.g. IACUC/investigator response)

AW: As explained in the presentation, PHS requirements focus on alleviation of pain and distress as cited in the US Government Principles, the PHS Policy, and the Vertebrate Animal Section of the grant application. While there is no specific requirement for a literature search, the PI typically has conducted literature searches in developing the study and preparing the grant application. The PI must abide by the provisions in those documents to address how pain and distress will be addressed. It is not a regulatory requirement to categorize non-USDA/DOD projects into pain categories.

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14) Some of these suggestions and alternatives would be very helpful to implement. Is there any indication that DOD will be willing to consider similar interpretations (e.g., lit searches for non-covered, non-Cat D/E animals)?

Institutions: There needs to be good communication to see why DOD has its current practices and whether they are serving a purpose for their organization.

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15) As a follow-up to the prior question on pro/retrospective classification....Can a PI prospectively classify animals in a higher pain classification to hedge any issues that may occur? For example, if it is "possible" that pain may not be completely relieved, should animals be classified as E instead of D?

BG: The regulations require that the reporting facility state the number of animals upon which research is conducted involving each pain category. If a PI is unsure, the facility should conduct a review or a pilot study or some other method to evaluate the project to make sure procedures involving animals will minimize discomfort, distress or pain. As a reminder, Column E animals are those for which the use of appropriate anesthetic, analgesic or tranquilizing drugs would have adversely affected the research and an explanation of procedures producing pain or distress and the reasons that drugs could not be used (Column E) must be attached to the annual report.

Institutions: It is important to note the Cat E is Animal use activities that involve accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, tranquilizing drugs; or other methods for relieving pain or distress are NOT used. If analgesics are being administered properly then it should be Cat D. Pain sensitivity may vary and if appropriate doses of analgesics are given then this should be Cat D and not re-categorized because a particular animal showed signs of pain with analgesia.

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16) If an investigator breeds animals to obtain a specific transgenic or knockout they are required to justify animals that may be bred but not used due to wrong genotype - is this required if an outside entity such as a Charles Rivers conducts the breeding for the investigator. Why or why not? What is the difference?

Institutions: In my experience this would be reviewed/approved by the contract breeder and the number that are produced and not used should be justified in a protocol.

AW: As an assured entity, Charles River is required to address the numbers of undesired genotypic animals produced in its records.

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17) In conducting grant congruence, the VAS section simply states that analgesics will be provided. How/why is this VAS section accepted as complete by NIH?

Institutions: I can't speak for NIH - I believe that this is because the IACUC protocol states the specifics and has to be reviewed and approved by the IACUC.

AW: OLAW will not answer this question as it is off topic. Because a detailed discussion of peer review was not part of the webinar, answering this question would not be helpful to the greater audience and could cause more confusion.

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18) Some of these items are 'required' in terms of the Guide for the Care and Use of Laboratory animals. The Guide states the number of animals should be statistically justified. How can that be done with a range of animal numbers?

Institutions: see question #5

AW: See #3, #10

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19) Will VMOs be trained and given this information as well on the animal numbers range item? for example, will this slide presentation be made available to VMOs? thank you.

BG: Yes

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20) For the removal of the lit search requirement for D/E procedures in non USDA species, does COGR know if those institutions who chose to remove this requirement are private vs. public institutions? Thank you.

Institutions: I don't know for sure but as noted above - there is still a requirement for consideration of alternatives and the 3 Rs.

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21) Is it ok then to just classify all animals on a protocol at the highest pain and distress category?

BG: The reporting facility should provide information that is as accurate as possible with regard to the pain categories. I can think of at least 3 reasons not to put animals in a high pain category just to avoid later reclassification.

For animals in Column E you must explain which procedures involved more than momentary pain or distress and why drugs could not be used. Having to explain that there was no procedure which caused more than momentary pain or distress would be confusing and more time consuming than correctly classifying the animal.

With accurate reporting, USDA inspections will be more streamlined. VMOs will conduct routine reviews of all animals and protocols related to animals reported in Column E.
The Annual Report numbers are provided to the public under the Freedom of Information Act. These numbers are often compared with prior years and with publications. Fluctuating or inflated pain classifications will call the accuracy and usefulness of the current report, prior reports, or the publications into question.

MG: On a protocol, it is more important to indicate which procedures are likely to cause more than momentary pain or distress. This enables the reviewers to consider whether alternatives have been considered and that all steps are being taken to minimize and/or eliminate pain and/or distress to the animals. At some point, for USDA covered species, there needs to be an indication of approximate number of animals used in B, C, D, and E.

Institutions: Agree with others comments - defaulting to the highest pain category is not recommended for the annual report. If they do this prospectively and correct it retrospectively for reporting then that could be ok.

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22) Do personnel reviews in an amendment require IACUC approval? if not, how do we enforce training and justify considering it a noncompliance when the individual begins work prior to being approved on a protocol?

BG: Assuring appropriate personnel qualifications is a requirement under the AWA but there is no requirement to track these in a protocol amendment. The IACUC can assure appropriate qualifications via the protocol process but they have the flexibility to assure that personnel are qualified in other ways as well.

MG: NOT-OD-14-126 includes personnel changes, other than the PI, as allowable administrative changes, not needing IACUC approval. See Other changes at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html . That should not preclude verifying training, which can be done by staff, and managing noncompliance.

Institutions: Training verification can be part of the administrative task before someone is added to a protocol. One way to limit work prior to approval is to limit access until training is complete.

AW: A change in personnel, other than the PI, must undergo an administrative review to ensure that all such personnel are appropriately identified, adequately trained and qualified, enrolled in occupational health and safety programs, and meet other criteria as required by the IACUC. (See https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html and https://olaw.nih.gov/guidance/significant-changes.htm

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23) Someone mentioned a series of questions asked at the time of 3-year review. Can you provide us with examples of those questions or templates?

MG: See PHS Policy IV.C.2.a-g.

Institutions: Some institutions ask for an update on alternatives & 3Rs considerations and a summary of experience with the protocol at triennial review. Other common areas of focus are: personnel changes, room changes, animal number adjustments, new aim/experiment, add/modify animal use procedures, change in strain/species.

AW: The three-year review must be a complete review in accordance with IV.C.1-4 of the PHS Policy.

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24) The earlier question is how to reconcile the use of approximate animals which is fuzzy and the use of statistics to establish group size, which is not. Despite the answers given today, there appears to be no way to rigorously assess sample size and also use approximate numbers. Any new thoughts?

Institutions: see #5 above.

AW: See all previous questions on this matter, #3, and #10.

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25) If we have an SOP with percentages allowable for USDA and non-USDA animals, is it okay to use VVC to change animals from Category C to Category D or E as long as all the approved protocol procedures remain the same?

BG: A change resulting in greater pain, distress or degree of invasiveness is a significant change and must be approved by DMR or FCR. You can use VVC to make changes in analgesia, euthanasia or procedures that do not result in greater pain, distress or degree of invasiveness.

MG: NOT-OD-14-126 does not allow an increase in pain, distress, or degree of invasiveness. See 1. a-b at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html .

Institutions: I agree with the above but the question is a little unclear - if the procedures are the same then it seems like that pain category would be the same - this may speak to MG comment above about categorizing a procedure. Also - if retrospective reporting places an animal in a higher pain category than anticipated then this is not a "non-compliance"…. BG: correct. Retrospectively moving an animal into a different category is not considered non-compliance.

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26) Betty, Are we able to 'renew' protocols triennially for USDA covered species?

BG: Yes, that is up to the IACUC. What you must do is conduct a continuing review of the activity no less than annually. The IACUC determines how best to conduct that continuing review.

MG: The USDA does not require a triennial review. It requires "continuing reviews … not less than annually;"

Institutions: agree

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27) Betty, Is there a reason to categorize an Antibody study using Freunds as Cat D if there have not been pain and distress issues.

BG: No, if there have not been any pain or distress issues with the procedure you are using it should be categorized as a C. In the past, Animal Care used Freunds projects as an example of a procedure that may cause more than momentary pain or distress because procedures using Freunds did cause pain but you should categorize the animals according to their actual experience.

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28) DOD continues to be the most burdensome regulatory body. Has that organization begun to consider how to reduce burden? As DOD funding is often used on non-USDA species, it becomes incredibly difficult for institutions to track, for example, which mouse protocols must follow DOD requirements versus those mouse protocols that do not. From talking with other institutions, we know this is a shared feeling across many institutions. Investigators have the most delay and over-burdensome additional review from DOD.

Institutions: See answers above.

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29) What were some of the alternatives to using annual renewals as Post-Approval Monitoring?

Institutions: There are several alternatives which can include regular check-ins with the research team and utilizing amendments and semiannual inspections as opportunities for updates.

AW: Continuing review may be accomplished by post-approval monitoring; semiannual review; laboratory visits by an IACUC coordinator or veterinarian; transmission of feedback to the IACUC from technicians, animal care staff, investigators (self-reports).

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30) Can the panel comment on the requirement for safety committee approvals. Specifically, is safety approval required prior to IACUC approval or could it be appropriate to allow a concurrent review and an institutional process to ensure the protocol is not initiated without both IACUC and Safety approval.

Institutions: Currently we do a concurrent process and do not do the final approval of the protocol until the safety approval is verified. If there is a system for preventing initiation of the study prior to safety approval then this should work.

AW: IBC reviews may be conducted concurrently with the IACUC review. Any relevant animal work should not be started until all required approvals have been obtained.

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31) Regarding the Pain/Distress Classification can the USDA speak to whether the annual report is intended to be a prospective or retrospective report? If retrospective, then does a protocol need to be classified in a pain category or only the animal records following procedures?

BG: Research facilities can report prospectively or retrospectively as long as animals that are originally classified in column C or D that should have been in Column D or E are appropriately reclassified.

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32) If the IACUC conducts a triennial review and notes items which should be updated/corrected, how are institutions handling this? What happens if the PI does not respond to the review items before its three year expiration date? Are expiration dates even necessary or as long as the IACUC had conducted its review is the requirement met?

MG: According to PHS Policy, for PHS/NSF funded projects must conduct "a complete review ... at least once every three years." The IACUC can put a hold, vote to withhold approval, or suspend the activity if the absence of said response does not allow the IACUC to complete its required review. At any rate, work cannot continue beyond 1,095 (365 x 3) days after the original approval date because the approval has expired.

Institutions: If the PI does not respond then the protocol expires and all work must stop. The IACUC must review and approve and approval is dependent on the PI incorporating changes.

AW: It is a best practice to include any minor changes that have been implemented in the revised protocols. Unapproved significant changes discovered during triennial review constitute noncompliance with the PHS Policy and are to be reported to OLAW. Proposed significant changes require IACUC review and approval. If the protocol expires prior to approval, the work must stop and the new changes are not to be implemented until approved. The expiration date is a definitive deadline and IACUC approval must be given before work can proceed.

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33) The Guide for the Care and Use states statistics are one way to justify numbers. AAALAC enforces this statement. They have not allowed estimates or based on previous experience.

Institutions: Statistics with estimates.

AW: This statement does not ask a question. See #3, 10 for discussion of this topic.

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34) RE: USDA Annual report...So does a protocol need to be labeled with a pain classification? If a study was expected to be a C no lit search was required. If the animals end up experiencing pain/distress is the expectation that the protocol would be revised to be Category E and a lit search included?

BG: There is no requirement to label a protocol with a pain classification. The Reporting facility can determine the best way to track animals for the Annual Report.

If no pain or distress was expected when the protocol was approved but the animals do experience more than momentary pain or distress, that is a significant change which should go back to the IACUC for review and approval. At that point, the IACUC must assure that procedures will avail or minimize pain and distress and that the PI has considered alternatives to procedures causing more than momentary pain or distress going forward. It's true that animals did experience pain or distress but unexpected results are in the nature of research. The facility would be considered to be in compliance as long as the PI and the IACUC took appropriate action as soon as they became aware of the situation.
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35) Re: VVC -- even if the procedure has been pre-approved by the IACUC and can be verified and approved by the Vet, is the expectation that an amendment is submitted to the protocol or can the procedure change be implemented without an amendment to the protocol?

MG: A PI cannot add a procedure to an approved protocol via VVC. The duration, frequency, or number of procedures performed on an animal can be amended under 2.c in NOT-OD-14-126. Although 'type' is included in that list, OLAW has stated that a new procedure cannot be added. See https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html .

Institutions: Anything that is added to the protocol via VVC needs to be properly recorded and incorporated into the protocol.

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36) If institutions are not requiring a triennial re-write, how are they ensuring PIs have re-considered alternatives to painful procedures, which must occur at least every 3 years?

BG: There is no requirement for the PI to rewrite the protocol but, if the institution requires a rewrite and resubmission of the protocol and considers the protocol to be new, the IACUC will have to determine that the PI has considered alternatives during the review of proposed activities. If, on the other hand, the IACUC conducts a continuing review of an ongoing study, a consideration of alternatives requirement applies only to new procedures that may cause more than momentary pain or distress.

Institutions: During a triennial review there are certain fields/questions that need to be updated - see #23

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37) Could you provide some guidance in documenting the process of DMR? This is in comparison of minutes for FCR.

MG: maintenance of reviewer worksheets and correspondence between the IACUC and the PI.

Institutions: Need to document that protocol was sent to full committee for comment, DMR assignment by the IACUC Chair and approval by DMR.

AW: One option is to document DMR actions in the FCR minutes listing the designated members and the outcome of the review. Any documents used by the DMR reviewers in requesting modifications to secure approval may be added to the IACUC records. The method of review for a given protocol must be documented along with the outcome of the review.

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38) For approximating animal numbers, how much "range" is considered acceptable by PHS and USDA?

BG: In determining the approximate number of animals to be used, the IACUC can determine what constitutes an appropriate 'range'.

Institutions: See # 9 above.

AW: This is up to the IACUC. An infinite upper limit is not acceptable. The range should incorporate loss of animals due to experimental or natural mortality. The low end of the range should ensure statistical significance.

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39) Sally mentioned practices at other institutions to minimize burden. Can she share these?

Institutions: These are summarized in the COGR report.

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40) The DMR documentation has to be via the minutes, including who performed the review. What if there are other IACUC records that document the person? Does reviewer name still need to go in the minutes?

BG: There is no USDA requirement to document the name of the reviewer in the IACUC minutes.

MG: Minutes are to document what happened at a meeting. As DMR happens outside the meeting, institutions need another mechanism such as maintenance of reviewer worksheets and correspondence between the IACUC and the PI.

AW: Any valid IACUC records that document who did the DMR and what the outcome was is acceptable. See # 37

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41) If approximate animal numbers are acceptable, why is it requested to count pups before they are weaned?

AW: Newborn pups are live vertebrate animals used or intended for use in research, research training, experimentation, or biological testing or for related purposes. Pups must be accounted for under the PHS Policy as soon as possible after birth although these numbers may also be approximate.

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42) Has there been feedback from institutes that have implemented the recommended burden reducing processes? Have any increases in non-compliance been noted? Do PIs and researchers find that these processes (e.g., VVC, DMR instead of FCR, approximating numbers) are helping to reduce burden for them?

MG: Absolutely! The IACUC staff have benefited significantly in a reduction of workload by the elimination of the requirement for PIs to submit an annual report. The IACUC benefits in the reduced effort of reviewing a triennial new submission vs a continuing review of an ongoing study. The PIs efforts have benefited in that VVC allows changes their research to be implemented within hours (sometimes minutes) without the unnecessary delay caused by process requirements of FCR and DMR.

AW: OLAW has received anecdotal responses regarding VVC and the majority have been positive in reducing wait times for implementing significant changes and reducing the burden of review on the IACUC. DMR and FCR have always been allowed as equivalent methods to review protocols and again anecdotal information of institutions using DMR points to a quicker turnaround in protocol approvals.

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43) If we do not classify non-USDA covered species into pain and distress categories, how can we ensure the public that we are adequately addressing animal welfare concerns for all species?

Institutions: There are different ways of categorizing studies/ procedures vs the USDA pain classifications. Some institutions use 2 categories (+/- pain/distress). Regardless whenever we are using animals we are required to consider the 3R's - alternatives and minimization of pain/distress.

AW: For PHS and NSF funded research, the IACUC is required to review activities according to PHS Policy IV.C.1.a-g and the US Gov't Principles. In addition, assured institutions must base their programs on the *Guide for the Care and Use of Laboratory Animals* (p.26) which requires the IACUC to review the following key aspects that address animal welfare:

- Impact of the proposed procedures on the animals' well-being
- Appropriate sedation, analgesia, and anesthesia (indices of pain or invasiveness might aid in the preparation and review of protocols);
- conduct of surgical procedures, including multiple operative procedures;
- Post-procedural care and observation (e.g., inclusion of post-treatment or postsurgical animal assessment forms);
- Description and rationale for anticipated or selected endpoints, and
- Criteria and process for timely intervention, removal of animals from a study, or euthanasia if painful or stressful outcomes are anticipated.

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44) Do institutions use generic protocols for repetitive studies, e.g., regulatory studies? These can reduce the review process by reducing the total number of protocols reviewed. Changes in some aspects may be done by minor amendment, as long as there are no expected changes in agent side effects.

Institutions: Some facilities may do this. Whenever possible it is useful to rely on procedures that are standardized across an institution.

AW: The IACUC must review and approve activities on a project specific basis taking into account a number of factors such as the aims of the study, consideration of alternatives, minimization of pain and distress. For routine aspects of research (e.g., species specific techniques for immunization and titer determinations during antibody production) IACUCs may approve SOPs that can be cited by investigators in their protocols to avoid needless repetition. SOPs should be reviewed by the IACUC at appropriate intervals (at least once every three years) to ensure they are up to date and accurate. (Also see https://olaw.nih.gov/guidance/faqs#F)

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45) Can you provide some examples of activities that might improve animal welfare? (if resources were freed up from burdensome activities)

Institutions: If resources were freed up then we could devote more resources to (1) alternatives development, (2) enrichment and training for animals when they need to be used in research and (3) increased recognition and compensation for animal caregivers. This would also free up time for the research community so that they could focus on their science and give them more time for innovation.

AW: Animal welfare is an ongoing responsibility for all parties involved in animal research. Animal care and use programs must be compliant with all federal policies and regulations. Burden reduction on the investigator is to lead to more time to do science rather than dealing with regulatory issues, some of which may be reduced by the methods discussed in this presentation. Reducing burden does not equal reducing animal welfare.

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46) Regarding OLAW NOT-OD-14-126, if a protocol has been approved by full committee for a particular genus of fish, bird, reptile, or amphibian. May we apply NOT-OD-14-126 to make species changes within the approved genus without full committee review? Our institution uses a lot of fish, and to do FCR for each change in species change can be burdensome.

MG: If your institutional process stipulates that amendments to protocols approved by FCR also must be reviewed by FCR, you don't have a choice other than to change your institutional process. Otherwise, VVC can be used to change genus if such changes are included in your VVC process and the veterinarian agrees to such a change.

*AW: Significant changes that require IACUC approval by FCR or DMR include change in species. Protocols may include a list of potential animals (such as a list of 20 fish species expected to be used in the proposed research) and then the PI is free to pick from this list. Additional changes in species not already included may be made by DMR.
For PHS supported studies, prior approval must be obtained from NIH regarding a change in species.

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47) Has COGR asked what percentage of institutions are requiring PI's to list the specific rodent strains/stocks they use?

Institutions: I haven't seen this question asked - answer from above - With the complex nature of genetically modified crosses we do not require each individual strain be listed. Any strain that is associated with abnormal phenotypes or special monitoring requirements should be listed.

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48) For Betty, if the protocol appropriately describes managing pain/distress and consideration of alternatives, if there any expectation for IACUCs or by VMOs that the PD classification be specifically described by the PI in the protocol (e.g. grouping numbers by category, etc.)?

BG: There is no requirement to label a protocol with a pain classification. The Reporting facility can determine the best way to track animals for the Annual Report. As you note, there is a requirement that the IACUC assure that the PI has considered alternatives to the painful or distressful procedure and I think that is what leads to classifying the protocols. Many facilities find that protocol classification makes annual reporting easier but it's entirely up to the facility how to track for Annual Reporting.

Webinar 2: Understanding Federal versus Institutional Research Requirements

Ara Tahmassian (AT) – Institutions Response
Sally Thompson-Iritani (STI) – Institutions Response
Axel Wolff (AW) – NIH OLAW Response
Betty Goldentyer (BG) – USDA Response
Molly Greene (MG) – IACUC/Investigator Response
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Gaylen Edwards (GE) – IACUC Investigator Response

Questions:

1) Many items listed as VVC review appear to be administrative to me- not major changes, eg. change in personnel other than PI?

MG: NOT-OD-14-126 codified the items you mention as allowable administrative changes. See Other changes at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html

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2) Were the same number of responses collected for each category of administrative burden?

MG: Yes, between 92-94 responses for each question.

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3) Do VVC changes ultimately go through an amendment if the team continues to use the changes?

MG: No. Once the veterinarian confirms the change is acceptable and allowable under VVC, the change can be incorporated into the approved protocol. This must be documented. See https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html .

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4) If a veterinarian approves a modification using VVC, but the change is not something previously approved by the IACUC, is this noncompliance?

AW: Yes, it is noncompliance if the modification constitutes a significant change that is conducted without IACUC approval. The veterinarian is not approving the modification but is serving as a subject matter expert to verify that compliance with the IACUC-approved policy is appropriate for the animals in the circumstance. (also, see #5)

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5) How are VVC-approved modifications supposed to be incorporated into the protocol?

MG: Documentation of such changes is required but how your institution manages this is not prescribed. Some places both the PI and the veterinarian send follow-up emails or reports as documentation.

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6) Do you often see an agent being added to a protocol as a VVC in coordination with an health and safety member, OR you see this more going to DMR?

GE: If it is a drug in the same class (eg xylazine and medetomidine) where an alpha 2 agonist is approved in the protocol, then yes, it could easily be approved by VVC. If it is a different experimental agent (eg novel therapeutic), it is difficult for the IACUC to anticipate use of novel agents and pre-approve. Therefore, it would likely go to DMR or FCR.

Institutions: If an agent is approved for a different procedure on a protocol and included in the Biological Use Authorization for the protocol then it may be added to another experiment/procedure via VVC. If it is not listed anywhere on the protocol and it requires EH&S approval then we would require it to go DMR/FCR.

AW: If the agent was not listed on an IACUC approved list, then the change must be reviewed by DMR or FCR. Depending on what the "agent" is, the veterinarian should review the pre-approved IACUC list of agents and confirm that individuals using the agent are trained in it use and there is no expected increase in pain or distress or increase in safety concerns for personnel.

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7) For DMR, it was mentioned about the quality of the reviewer, other than IACUC training is there regulatory requirements for reviewer qualifications. Specifically I wonder if a veterinarian is required, or could veterinary staff be used as well/instead, e.g. animal health technicians, etc.

GE: This depends on the species and level of pain and distress. The AWA requires the involvement of a veterinarian in procedures that may cause more than momentary or slight pain and distress (Sect. 2.31 (d)(1)(iv)(B)). For non-AWA covered species, the Guide has multiple "should" statements strongly recommending veterinary review. My experience is that most programs do have veterinary review for all species, particularly for protocols that may cause more than momentary or slight pain and distress.

Institutions: I agree with Gaylen on this. Programs that I have been involved with have veterinary consultation/review involved with all species/protocols. The degree of involvement varies depending on the study and an initial consultation always occurs.

*AW: The PHS Policy states for DMR that "at least one member of the IACUC, designated by the chairperson and qualified to conduct the review, shall review those research projects…" This person does not have to be a veterinarian. Qualified IACUC members, such as a scientist, a veterinarian, or animal health technician would all be eligible if they are knowledgeable about the information in the protocol. The IACUC may invite consultants to assist with the review of complex issues. Consultants may not approve or withhold approval of an activity or vote with the IACUC unless they are also members of the IACUC.

BG: Yes, for procedures that may cause more than momentary pain or distress, the planning consultation with the AV, or his/her designee, is a requirement. Veterinary review, or review by animal health staff, is up to the IACUC and can definitely be scaled based on the species and the study.

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8) Is there a regulatory requirement for a veterinarian to pre-review protocols with potential pain or distress? If so does that require a veterinarian or could veterinary staff, e.g. Animal Health Technician, do this instead?

MG: USDA 2.31.d.1.iv: "Procedures that may cause more than momentary or slight pain or distress to the animals will: … (B) Involve, in their planning, consultation with the attending veterinarian or his or her designee;"

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9) Is continuing review responsibility of the PI or IACUC?

MG: PHS: "**The IACUC shall conduct continuing review** of each previously approved, ongoing activity covered by this Policy at appropriate intervals as determined by the IACUC, including a complete review in accordance with IV.C.1.-4. at least once every three years."

USDA: "**The IACUC shall conduct continuing reviews** of activities covered by this subchapter at appropriate intervals as determined by the IACUC, but not less than annually;"

Responsibilities of the PI are not discussed

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10) Has VA national leadership weighed in about which, if any of the items discussed, may be eliminated in the VA?

MG: None of us are affiliated with the VA. But I understand the VA uses the PHS Policy and we were discussing what is and is not currently required. We did not discuss any impending or proposed changes by PHS.

Naomi Charalambakis (FASEB Staff): After speaking with VA staff (April 2019), they are currently having ongoing discussions of their own to update and streamline agency policies for animal research with those of NIH, USDA, FDA, etc.. Updates to their website and guidance documents will be released in the coming months. They specifically noted that these talks were inspired because of this webinar series!

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11) So an increase in animal numbers is not considered a major modification? And, for these VVC approved via a phone call, and you request an email, how to you keep everything together for then an actual major modification later on that protocol if the changes aren't made directly to the original protocol? So you are saying changes are made after the fact?

MG: An increase in animal numbers is a "significant change that may be handled administratively". See item 3 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html. Documentation of this change is required but how your institution manages this is not prescribed. Some places both the PI and the veterinarian send follow-up emails or reports as documentation.

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12) What are the best approaches to incorporate VVC changes into the protocol?

MG: Documentation of changes made is required but how your institution manages this is not prescribed. Some places the both the PI and the veterinarian send follow-up emails or reports as documentation.

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13) Can incisional repair be included in a VVC approval? Or does it need to be written in the protocol?

MG: If the incisional repair is clinically necessary for the welfare of the animal, yes, it may be included in a VVC approval based on an IACUC-approved policy. However, changes for clinical care purposes for a particular animal may simply be a conversation between the vet and the PI. If it is an additional procedure for research purposes rather than clinically necessary, no it may not be handled by VVC. NOT-OD-14-126 does not allow procedures to be added using the VVC process. See https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html .

Institutions: This would depend on the need for the incisional repair. If this is a single occurrence then it is usually dealt with as a clinical procedure by the veterinarian. If an incisional repair is required as part of the protocol then this would need to be justified and approved by DMR/FCR if it could increase pain/distress.

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14) How are the changes to the protocol documented if VVC is used?

MG: Documentation of changes is required but how your institution manages this is not prescribed. Some places the both the PI and the veterinarian send follow-up emails or reports as documentation.

Institutions: It is important to document the VVC and ensure that it is incorporated or appended to the approved protocol so that it carries forward with future approvals.

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15) What about an updated literature search for the three year rewrite?

BG: There is no requirement for the PI to rewrite the protocol but, if the institution requires a rewrite and resubmission of the protocol and considers the protocol to be new, the IACUC will have to determine that the PI has considered alternatives during the review of proposed activities. If, on the other hand, the IACUC conducts a continuing review of an ongoing study, a consideration of alternatives requirement applies only to new procedures that may cause more than momentary pain or distress.

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16) What is considered a "change in study objectives" in determining eligibility for VVC? What about for example change in age of animal studied, or change in agent used to induce a similar outcome?

MG: Study objective is the aim of the research, i.e., what is being studied or researched in broad terms. Change in age may not be a change in the study objective nor is change of agent used to induce a similar outcome. The question is a little vague, but if the goal of the study becomes the study of the aging processes, then the objective of the study may have changed.

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17) You cited the literature search as a requirement for AWA species. My understanding is that lit searches are in APHIS guidance, but not required. Please explain your use of the word "required."

BG: Policy #12 is under review at this time. In absence of policy guidance it is important to refer back to the regulation itself. Section 2.31(d)(1)(ii) requires that the IACUC determine that the PI has considered alternatives to procedures that may cause more than momentary or slight pain or distress during the review of proposed activities or significant changes and has provided a written narrative of the methods and sources used to determine that alternatives were not available.

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18) I thought that I heard that triennial review was not required, but that doesn't seem consistent with PHS Policy (IV.C.5). Could you elaborate on the efficiencies we can apply to triennial review?

MG: PHS Policy IV.C.5. "**The IACUC shall conduct continuing review** of each previously approved, ongoing activity covered by this Policy at appropriate intervals as determined by the IACUC, **including a complete review** in accordance with IV.C.1.-4. at least once **every three years**." What is not required is a re-write of the protocol or a new submission. The IACUC is charged with continuing review, the PI is not required to do anything. Many places are asking the PI to review and make changes to the existing protocol which the IACUC then reviews using IV. C.1-4, specifically IV.C.2.a-g.

Institutions: It is helpful for the PI to sign a certification statement when the protocol is submitted to the IACUC for the review.

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19) Follow-up question - has OLAW said they agree with Molly's interpretation on triennial review? From what I can tell our Assurance applies to all research, except for some reporting requirements.

MG: Watch the 1st webinar (click for link) and you will hear what Axel Wolff had to say on slides 8-10.

- Slide 8:
  "PHS Policy does not require a rewrite—just a review of an ongoing study:
  PHS Policy IV.C.5: "The IACUC shall conduct continuing review
  of each previously approved, ongoing activity...,
  including a complete review in accordance
  with IV.C.1.-4 using DMR or FCR".

- Slide 10:
  "This triennial review is interpreted by OLAW as a requirement for de novo review
  • criteria and procedures for review specified in IV.C of the PHS Policy must be applied not less than once every three years.
  • The 3 year renewal protocol document does not need to be completely re-written because it is not a new project. It is a renewal of ongoing activity.
  • updates and changes need to be included
  • obsolete information should be removed.
  • It is a best practice to incorporate added amendments (although, they can also be attached)
  • This document should then be reviewed by the IACUC in accordance with IV.C.1-4 using DMR or FCR".

What your Assurance says is what your institution submitted to OLAW. You can amend your Assurance and report changes in your Annual Report to OLAW.

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20) Are we to understand that changes in personnel (other than the PI), corrections of typos and/or contact information now require a VCC? We used to approve these administratively and involve only office staff. If the veterinarian is now required to approve these amendments, this would seem to add to regulatory burden.

MG: NOT-OD-14-126 codified the items you mention as allowable administrative changes. See Other changes at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html
AW: Only certain significant changes require Veterinary Verification and Consultation. Others can be handled administratively by someone other than a veterinarian.

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21) Re: VVC... If the IACUC has pre-approved a standard procedure library, can those SPs be added by VVC, as long as the pain/distress is not increased?

MG: A procedure may not be added using VVC, only with FCR or DMR. The duration, frequency, or number of procedures performed on an animal may be amended under 2.c in NOT-OD-14-126. Although 'type' is included in that list, OLAW has stated that a new procedure cannot be added. See https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-126.html.

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22) What is required for field projects that are collect/euthanize and no other procedures are done on the live animal? Do most institutions require a full protocol?

MG: From Bob Sikes *(Facility Director and IACUC Chair at University of Arkansas Little Rock*):

First, check your OLAW Assurance. If the activities are covered by the assurance, whether because of funding or because the institution has elected to write their assurance so that it applies to all activities regardless of the source of funding, then these activities would require a protocol and review by the IACUC since the proposed activities exceed the limits of what OLAW considers a "field study" though they do not use that specific term. See OLAW FAQ A.6 on applicability of the PHS policy (https://olaw.nih.gov/guidance/faqs).

If not under the assurance and it involved USDA covered species, based only on the brief description you have provided, the IACUC could consider this to meet the "field study" exemption provided they have also determined the method of death to constitute humane euthanasia. In that case, a brief review that provide them sufficient information to make a determination that it did indeed meet the regulatory definition of a field study and the form of death was humane euthanasia would suffice. Under these circumstances the animals also would not be included on the institution's annual report.

Now, stepping beyond regulatory requirements, if the goal is to publish from the specimens or data collected, many journals are now requiring a statement of ethical review as a condition for publication, so without an IACUC review, the investigators might be limiting their options. (see Mulcahy, 2017, The Animal Welfare Act and the conduct and publishing of wildlife research in the United States).

Thus, from a practical standpoint and even if not covered by a PHS assurance, most IACUCs definitely would review the activities but may not require a full protocol.

AW: Field studies also need to address occupational health and safety.

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23) If you have a protocol with >20 amendments approved over the first three years how do you not rewrite the protocol at the three year renewal if over 50% of the work has been completed.

MG: Most institutions now incorporate amendments directly into the existing protocol. In your example, a rewrite may be the best way to proceed, but it is not required. Many places are asking the PI to review and make changes to the existing protocol which the IACUC then reviews using IV. C.1-4, specifically IV.C.2.a-g.

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24) If you allow investigators to "clone" their protocol for three year renewal how do you determine there is no unnecessary duplication of work?

MG: Because it is an ongoing study that is probably no more unnecessary than the previous 3 years. Please note the key word is unnecessary. In addition, the unnecessary duplication attestation is a USDA requirement and the USDA does not have a three year review requirement. It requires annual review.

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25) Question for Molly do you archive all of the versions of the protocols as they are replaced during the amendment process so there is history of the work?

MG: Yes.

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26) As the IO how do you move these initiatives forward when the IACUC says they understand the flexibility but believe it is best to not implement them and because they are the IACUC they can't be made to change.

JRH: This would be a good time to talk about shared goals of animal welfare and moving research forward. Organizations and their people often resist change to maintain the status quo. In these conversations the phrase I often use is: "The only constant is change". If we, as an organization/institution, are doing things we don't have to do, then the onus is on the resistant group to justify why those processes and procedures are important to keep doing. It is not the responsibility of the change agent to justify why the changes should be made if they do not compromise animal welfare, are not required, and potentially save time and money. In the end, everyone including the animals are winners. If there is still resistance after rational discussion, then it may be time to reconstitute the IACUC if people are not thinking about how they can constantly improve their processes.

I would add that the IACUC is advisory to the IO. It is a challenge for IOs to know what they need to know and to know it as well as the IACUC and the veterinarians. Find another IO to consult with. Read the FASEB report and especially the COGR report which goes into some detail about what is not required. Consult with someone who is or has recently been on the AAALAC Council for Accreditation. You do not need to be from an AAALAC accredited institution to seek their advice.

In addition, some IACUC staff and attending veterinarians see maintaining the status quo as protecting their jobs. Continuous improvement is a well-established principle in management practices. Very few organizations see the status quo as an improvement. Our IACUC staff found big reductions in their workload as we introduced these changes which were important because we aren't getting more staff.