REDUCING ADMINISTRATIVE BURDEN FOR RESEARCHERS: ANIMAL CARE AND USE IN RESEARCH

A Report by the

21ST Century Cures Act Sec. 2034(d) Working Group

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21st Century Cures Act Section 2034(d) Working Group

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Executive Summary

Title II, Section 2034(d), of the 2016 21st Century Cures Act (21CCA) directed the National Institutes of Health (NIH), in collaboration with the United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA), to complete a review of applicable regulations and policies for the care and use of laboratory animals and to make revisions, as appropriate, to reduce administrative burden on investigators while maintaining the integrity and credibility of research findings and protection of research animals. The Act instructs NIH to: (1) seek the input of experts, if appropriate; (2) identify ways to ensure applicable regulations and policies are not inconsistent, overlapping, or unnecessarily duplicative; (3) take steps to eliminate or reduce identified inconsistencies, overlap, or duplication among such regulations and policies; and (4) take other actions, as appropriate, to improve the coordination of regulations and policies with respect to research with laboratory animals.

NIH, USDA, and FDA convened a Working Group of federal subject matter experts that carried out a review and prepared a report of its recommendations as directed in the 21CCA.

To identify inconsistent, overlapping, and unnecessarily duplicative regulations and policies, the Working Group reviewed published reports, communications, and surveys highlighting the regulations and policies that contribute to researchers' administrative burden (Section 1, page 2); conducted listening sessions and met with organizations and stakeholders (Section 2, page 3); and issued a Request for Information (RFI) and analyzed stakeholder responses (Section 3, page 4). Appendix 1. Analysis of Key Findings from the Reports, Communications, and Surveys presents a condensed description of the key findings from the eight reports, communications, and surveys; the Working Group's analysis; and proposed actions. Appendix 2. Analysis of Responses to the Request for Information presents a summary of the public responses received for the eleven RFI topics, the Working Group's analysis, and proposed actions.

The Working Group identified the following areas in which there is opportunity to reduce administrative burden: semiannual inspections by Institutional Animal Care and Use Committees (IACUC), animal activities (protocol) review, and institutional reporting. Recommended steps to reduce duplicative regulations and policies are provided on page 5.

The Working Group identified the following areas in which there is opportunity to improve coordination: guidance on federal standards, agency harmonization, and training and resources. Recommended actions to improve coordination of regulations and policies are provided on page 6.

Appendix 3 lists the acronyms used in the report.

In the coming years, NIH, USDA, and FDA intend to make progress on the steps and actions described in this report and will identify additional ways to protect animal welfare while reducing unnecessary administrative burden on researchers.

Introduction

The 21st Century Cures Act (21CCA), Public Law 114-255, is comprehensive legislation intended to accelerate the research and drug approval process and address the opioid epidemic and mental illness. The legislation provides NIH with critical tools and resources to advance biomedical research across the spectrum, from basic research studies to advanced clinical trials of promising new therapies. Included in 21CCA are provisions aimed at reducing administrative burden on the research community. The legislation requires the conduct of activities to promote the development of researchers, including evaluation and oversight of existing programs. Section 2034(d) of 21CCA directs NIH, USDA, and FDA to: "[R]eview applicable regulations and policies for the care and use of laboratory animals and make revisions, as appropriate, to reduce administrative burden on investigators while maintaining the integrity and credibility of research findings and protection of research animals." Section 2034(d) then identifies specific activities expected by Congress:

1. identify inconsistent, overlapping, and unnecessarily duplicative regulations and policies with a focus on inspection and review requirements;
2. take steps to reduce same; and
3. take actions, as appropriate, to improve coordination of regulations and policies with respect to research with laboratory animals.

The NIH, USDA, and FDA 21st Century Cures Act Section 2034(d) Working Group (Working Group), composed only of federal employees, has prioritized its work in terms of three specific directions: (1) identifying overlapping regulations and policies, (2) taking steps to reduce these regulations and policies, and (3) taking actions to improve coordination, as directed by Congress.

This report outlines the efforts of the Working Group and others within the federal government and the proposed recommendations to reduce the administrative burden associated with research activities involving laboratory animals while maintaining appropriate protections and scientific integrity.

Review of Applicable Regulations and Policies to Identify Inconsistent, Overlapping, and Unnecessarily Duplicative Regulations and Policies

The Health Research Extension Act of 1985 (Public Law 99-158; https://olaw.nih.gov/policies-laws/hrea-1985.htm) provides the legislative mandate for the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (Policy; https://olaw.nih.gov/policies-laws/phs-policy.htm). The Policy establishes standards for the proper care and treatment of animals used in research, and for the organization and operation of animal care committees. The Policy applies to the use of live, vertebrate animals in any activity supported or conducted by PHS agencies and US Department of Health and Human Services components. The NIH Office of Laboratory Animal Welfare (OLAW) has been delegated authority by the NIH Director for the general administration and coordination of the PHS Policy.

The Animal Welfare Act (AWA) directs USDA to ensure the humane care and treatment of certain animals sold for use as pets, or used in research, public exhibition, or commercial transport. USDA, through the Animal and Plant Health Inspection Service (APHIS) Animal Care (AC) program, implements the AWA and Animal Welfare Regulations found in the Code of Federal Regulations (CFR), Title 9, Chapter 1, Subchapter A, Parts 1, 2, and 3.

FDA promulgates Good Laboratory Practice (GLP) regulations (21 CFR Part 58; https://www.ecfr.gov/cgi-bin/text-idx?SID=f60982d572e6c171f9473aa5fab7a6ef&mc=true&tpl=/ecfrbrowse/Title21/21cfr58_main_02.tpl) under the Federal Food, Drug, and Cosmetic Act and Public Health Service Act. The GLP regulations establish administrative standards for the conduct of nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by FDA.

To identify inconsistent, overlapping, and unnecessarily duplicative regulations and policies, the Working Group:

1. reviewed published reports, communications, and surveys that address inconsistent, overlapping, or duplicative regulations (including the areas of inspection and review requirements) that contribute to researchers' administrative burden;
2. conducted listening sessions and met with organizations and stakeholders; and
3. issued a Request for Information (RFI) in March 2018 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-152.html) to stimulate engagement with stakeholders concerning possible actions the agencies should consider for improving coordination and harmonization of regulations and policies.

The following sections highlight the outcomes of this review.

1. Reports, Communications, and Surveys Reviewed

The following documents were reviewed by the Working Group:

- Rebuttal to Federation of American Societies for Experimental Biology's Reforming Animal Research Regulations, February 2018, People for the Ethical Treatment of Animals, https://olaw.nih.gov/sites/default/files/DOC_02082018_Peta.pdf.
- Animal welfare regulations must not be compromised to comply with the goals of the 21st Century Cures Act, January 2018, Humane Society of the United States and Humane Society Legislative Fund, https://olaw.nih.gov/sites/default/files/DOC_01082018_HS.pdf.
- Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden, 2017, report of an April 17, 2017 workshop organized by Federation of American Societies for

Experimental Biology (FASEB), the Association of American Medical Colleges (AAMC), and the Council on Governmental Relations (COGR), with assistance from the National Association for Biomedical Research (NABR), http://www.faseb.org/Portals/2/PDFs/opa/2017/FASEB-Animal-Regulatory-Report-October2017.pdf.

- Revising the Requirements for Prompt Reporting Under PHS Policy IV.F.3., 2017, NABR, https://olaw.nih.gov/sites/default/files/DOC_2017_NABR.pdf.
- Optimizing the Nation's Investment in academic Research: A New Regulatory Framework For The 21st Century, 2016, National Academies, https://www.nap.edu/catalog/21824/optimizing-the-nations-investment-in-academic-research-a-new-regulatory.
- Reducing Investigators' Administrative Workload for Federally Funded Research, 2014, National Science Board, National Science Foundation, https://www.nsf.gov/pubs/2014/nsb1418/nsb1418.pdf.
- 2012 Faculty Workload Survey Research Report, 2014, Federal Demonstration Partnership (FDP), https://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_087667.pdf.
- Findings of the FASEB Survey On Administrative Burden, 2013, FASEB, http://www.faseb.org/portals/2/pdfs/opa/6.7.13%20FASEB%20NSB%20Survey%20findings.pdf.

Appendix 1 contains a summary of the key findings in the reports, communications, and surveys evaluated by the Working Group. It includes the Working Group's analysis and addresses the impact of the findings on animal welfare and scientific integrity, or where statutory changes are required.

2. Listening Sessions and Meetings with Organizations and Stakeholders

The Working Group held listening sessions and meetings leading up to the release of the RFI to explain the requirements in 21CCA, Section 2034(d); provide updates on the Working Group's progress; and encourage the research community, other stakeholders, and the public to provide ideas for how to meet the requirements. In many cases the listening sessions were part of presentations by Working Group members at regional and national conferences and workshops. The slides presented and summaries of comments and meeting notes, where available, can be found at https://olaw.nih.gov/21st-century-cures-act.htm.

The following listening sessions and meetings were held:

- New Jersey Association for Biomedical Research, IACUC 24 Conference, September 22, 2017, Session: Hot Topics in Regulatory Compliance, Working Group member: Patricia Brown
- 68th American Association for Laboratory Animal Science National Meeting, October 17, 2017, Session: Adapting to Change in the Animal Research Oversight Environment, OLAW Update, Working Group member: Patricia Brown
- Scientists Center for Animal Welfare, Winter Conference, December 4, 2017, Session: OLAW Update, Working Group member: Patricia Brown
- Federal Demonstration Partnership Forum, Government-University-Industry Research Roundtable of the National Academies, 21st Century Cures Act NIH-USDA-FDA Listening Session on Animal Research, January 9, 2018, Working Group members: Patricia Brown, Estella Jones, Betty Goldentyer
- AAALAC International Council Teleconference Meeting, January 29, 2018, Working Group members: Patricia Brown, Estella Jones, Betty Goldentyer
- Question and Answer Session with the Animal Welfare Institute, Humane Society Legislative Fund, Physicians Committee for Responsible Medicine, and Humane Society of the United States, March 12, 2018, Working Group members: Patricia Brown, Estella Jones, Betty Goldentyer
- Public Responsibility in Medicine and Research, 2018 IACUC Conference, March 21, 2018, Working Group member: Patricia Brown

3. Public Comments to Request for Information

The Working Group sought input from interested stakeholders on proposed actions that the agencies identified to improve coordination and harmonization of regulations and policies through a Request for Information issued in NIH Guide Notice NOT-OD-18-152, published March 14, 2018 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-152.html and published in a Federal Register Notice at https://www.federalregister.gov/documents/2018/03/14/2018-05173/laboratory-animal-welfare-coordination-and-harmonization-of-regulations-and-policies.

Information requested in the RFI was:

A. Input on the following proposed actions that the agencies are considering:
    1. Allow investigators to submit protocols for continuing review using a risk-based methodology.
    2. Allow annual reporting to OLAW and USDA on the same reporting schedule and as a single report through a shared portal.
    3. Harmonize the guidance from NIH and USDA to reduce duplicative considerations of alternatives to painful and distressful procedures.
    4. Provide a minimum 60-day comment period for new OLAW policy guidance.
    5. Other approaches not previously mentioned.
B. Feedback on whether the following tools and resources are or would be helpful in reducing burden on investigators:
    1. Encourage the use of sections of the AAALAC International (AAALAC) program description in applicable parts of the OLAW Animal Welfare Assurance, for institutions accredited by AAALAC.
    2. Encourage the use of the FDP Compliance Unit Standard Procedures (CUSP) as a repository of best practices for standard procedures used for research with animals.
    3. Encourage the use of the IACUC Administrators Association (IAA) repository of best practices by IACUCs.
    4. Encourage the use of new or existing tools to streamline protocol review through use of Designated Member Review (DMR), DMR subsequent to Full Committee Review (FCR), and/or Veterinary Verification and Consultation (VVC).
    5. Expanded IACUC training activities that focus on reducing burden on investigators.
    6. Other tools or resources not previously mentioned.

In response to the RFI, the Working Group received approximately 19,240 comments from stakeholders including researchers, academic and research institutions, animal welfare advocacy groups, scientific and professional societies and associations, other not-for-profit organizations, and the public. The Working Group appreciated the interest in the proposed actions and the time and effort taken to provide comments. The Working Group carefully considered the comments when developing the recommendations.

Overview of Public Comments

A significant majority of the comments from the research community were supportive of the proposed actions. This support was balanced by concerns presented by stakeholders from animal advocacy groups and the public. Appendix 2 presents a summary of the responses received to the eleven RFI topics with Working Group analysis and proposed actions. Due to the volume of responses received, similar comments were combined for brevity and efficiency. Comments that were not responsive to topics presented in the RFI are not included. Working Group responses that apply to multiple comments have been duplicated to allow commenters to easily identify the response to their specific concerns.

Recommended Steps to Reduce Duplicative Regulations and Policies with a Focus on Inspection, Review, and Reporting Requirements

The Working Group was charged with considering steps to reduce inconsistent, overlapping, or unnecessarily duplicative regulations and policies with a focus on inspection and review requirements. The Working Group identified several opportunities to reduce administrative burden based on review of reports, communications, and surveys; comments during listening sessions and meetings with stakeholders; and review of the responses to the RFI.

Inspections

- Both the Health Research Extension Act and the AWA require the IACUC to inspect animal care and use facilities, including sites used for animal surgeries, every six months. A change in the frequency of IACUC inspections would require statutory changes to both laws and has a strong likelihood of negatively impacting animal welfare. The PHS Policy allows flexibility in how and by whom the inspections are conducted. NIH in coordination with USDA will develop guidance to address existing flexibilities while fulfilling the purposes of the Acts.
- Section 2143(b)(3) of the AWA requires the IACUC to inspect, at least semiannually, all animal study areas and animal facilities of such research facility, and review as part of the inspection –(A) practices involving pain to animals, and (B) the condition of animals, to ensure compliance with the provisions of the AWA to minimize pain and distress to animals. Exceptions to the requirement of inspection of such study areas may be made by the Secretary if animals are studied in their natural environment and the study area is prohibitive to easy access.
- USDA allows flexibility in how and by whom the semiannual inspections are conducted. For example, AAALAC site visits that are consistent with section 2.31(c) of the Animal Welfare Regulations may be counted as one of the IACUC semiannual inspections.

Protocol Review

- The agencies plan to review and enhance current resources to support IACUC use of existing options that streamline protocol review and significant changes to approved protocols. This includes updated resources to encourage the use of DMR for low-risk activities and for three-year *de novo* review.
- The agencies plan to provide updated resources on what is exempt from IACUC review.
- NIH OLAW plans to review and update the guidance on non-pharmaceutical grade compounds to further clarify the options for IACUC review.
- USDA will propose, through notice and comment rulemaking, a regulatory change to Title 9 Chapter 1, Subchapter A-Animal Welfare, Section 2.31(d)(5), to remove the requirement that IACUCs conduct "continuing reviews of activities covered by [the Animal Welfare Act] at appropriate intervals . . . but not less than annually," and, instead, insert a requirement that IACUCs conduct a three-year *de novo* review of activities. IACUCs would continue to review, approve, require modification to, or withhold approval of significant changes regarding the care and use of animals in ongoing activities, as required by 9 CFR §§ 2.31(d)(7), 2.31(e). The regulatory change aligns USDA and NIH requirements and reduces the time and effort dedicated to reviewing protocols on an annual basis, while retaining the benefits of a thorough *de novo* review every three years and ongoing review of any significant changes. The IACUC may choose to review a protocol at an interval more frequently than three years as part of a program review.

Reporting

- NIH OLAW and USDA plan to allow annual reporting to both agencies on the same reporting schedule. The agencies will explore the development of a single reporting portal.
- NIH OLAW plans to change the instructions to the domestic Animal Welfare Assurance to support the use of AAALAC program description elements, thereby enabling consistency and limiting the rewriting

of responses relevant to both documents. NIH OLAW plans to coordinate with AAALAC about options for harmonizing documents to meet both organizations' requirements.

- NIH OLAW plans to review the guidance in NIH Guide Notice NOT-OD-05-034 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-034.html) on reporting requirements to refine and update examples of reportable situations, examples of situations not normally reported, the timeframe for reporting, and the information to be reported. Provision of the grant number in the noncompliance report will also be reevaluated.
- USDA recently developed an online portal for submitting annual reports. USDA included the research community in planning and developing the system. An online annual reporting system will streamline data submission.
- USDA intends to pursue a regulatory change to Section 2.30(a)(1) to eliminate the need to renew the registration every three years. The annual report will be updated to contain sufficient information to update USDA records, and no further information regarding the registration would be required.

Actions to Improve Coordination of Regulations and Policies

The Working Group was charged with considering actions to improve coordination of regulations and policies with respect to research involving laboratory animals. The Working Group identified several opportunities to improve coordination based on review of reports and surveys, comments during listening sessions and meetings with stakeholders, and review of the responses to the RFI.

Guidance on Federal Standards

- NIH OLAW plans to provide a minimum of 60 days for comments regarding significant policy guidance. This will include any new interpretations of the PHS Policy, the National Academy of Sciences (NAS) *Guide for the Care and Use of Laboratory Animals* (*Guide*), or the AVMA (American Veterinary Medical Association) Guidelines for the Euthanasia of Animals. Such guidance will focus on high risk animal welfare concerns affecting institutions.
- NIH OLAW plans to review its disclaimer concerning current guidance to emphasize that "unless specific statutory or regulatory requirements are cited, the guidance should be viewed as recommendations in that an institution may use an alternative approach if the approach satisfies the requirements of the PHS Policy."
- USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service. USDA will include a statement in its policy manual to explain that such policies are clarifications or interpretations of the AWA and Animal Welfare Regulations, which are the only legally binding requirements.

Agency Coordination

Although outside the scope of 21CCA, Section 2034(d), NIH OLAW, in coordination with USDA, plans to engage with the Department of Defense and the Department of Veterans Affairs about options for harmonizing requirements to reduce administrative burden on investigators who receive support for research with animals from multiple federal agencies.

Training and Resources

- NIH OLAW, in coordination with USDA, will support the continued development of industry-led training and resources to assist institutional leadership, IACUC members, and IACUC administrators in reducing administrative burden on investigators.
- NIH OLAW, in coordination with USDA, will continue to support the efforts of the IAA to create a repository of IACUC best practices. After the repository is piloted, NIH OLAW, in coordination with USDA, plan to offer resources to IACUCs to integrate the best practices into their institutional

processes to reduce administrative burden on investigators. Use of the repository would be optional and open-access.

- NIH OLAW, in coordination with USDA, will continue to support the efforts of the FDP members to create CUSP as a repository of best practices for standard procedures used for research with animals. After the CUSP repository is piloted by FDP institutions, NIH OLAW, in coordination with USDA, plan to offer resources to IACUCs to integrate CUSP into their institutional processes to reduce administrative burden on investigators. Use of the CUSP repository would be optional and open-access.
- NIH OLAW will consider updates to simplify its sample animal study protocol form and pilot the revised protocol form through FDP.
- NIH plans to consider new website resources in coordination with USDA.

Conclusion

Research regulations and policies are necessary to codify and enforce the expectations of the American public relative to how animals are used in biomedical research, teaching, and testing. For over fifty years and thirty years respectively, the Animal Welfare Act and Regulations and the Public Health Service Policy on Humane Care and Use of Laboratory Animals have provided a reasonable balance between expanding the knowledge base in medical and associated sciences to enhance the nation's economic wellbeing and ensure a continued high return on the public investment in research and protecting the welfare of the animals used in these endeavors. However, certain existing requirements consume researcher time and are due for review. In this effort, the agencies will continue to promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

In the coming years, NIH, USDA, and FDA intend to make progress on the steps and actions described in this report and will identify additional areas to protect animal welfare while reducing unnecessary administrative burden on researchers.

Appendix 1. Analysis of Key Findings from the Reports, Communications, and Surveys

Reports, Communications, and Surveys on Reducing Administrative Burden to Researchers and Research Institutions Reviewed by the Working Group

The following reports, communications, and surveys were reviewed by the Working Group:

Rebuttal to Federation of American Societies for Experimental Biology's Reforming Animal Research Regulations, 2018
In response to the 2017 workshop report from the Federation of American Societies for Experimental Biology (FASEB), the Association of American Medical Colleges (AAMC), the Council on Governmental Relations (COGR), and National Association for Biomedical Research (NABR), the People for the Ethical Treatment of Animals (PETA) provided recommendations to the Working Group to reduce administrative burden.

Animal welfare regulations must not be compromised to comply with the goals of the 21st Century Cures Act, 2018
In response to the 2017 workshop report from FASEB, AAMC, COGR, and NABR, the Humane Society of the United States and the Humane Society Legislative Fund provided comments to the Working Group on the report and made recommendations for simplifying regulations related to animal welfare.

Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden, 2017
This is a report of an April 17, 2017 workshop organized by FASEB, AAMC, COGR, and with assistance from NABR.

Revising the Requirements for Prompt Reporting under PHS Policy IV. F. 3, 2017
In June 2017, NABR provided recommendations to NIH OLAW to update current guidance for reporting a serious or continuing noncompliance with the PHS Policy or a serious deviation from the provisions of the National Academy of Sciences (NAS) *Guide for the Care and Use of Laboratory Animals* (*Guide*).

Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century, 2016
A panel convened by the NAS provided a comprehensive review identifying how a researcher's time is spent complying with regulations. The NAS authors offered several specific recommendations concerning oversight of research with animals.

Reducing Investigators' Administrative Workload for Federally Funded Research, 2014
In December 2012, the National Science Board of the National Science Foundation convened a Task Force on Administrative Burdens. The Task Force issued a Request for Information (RFI) to identify which federal agency and institutional requirements contribute most to Principal Investigators' (PIs) administrative workload and conducted a series of roundtable discussions with faculty and administrators. The most frequently reported areas associated with high administrative workload were financial management; the grant proposal process; progress and other outcome reporting; human subjects research and institutional review boards (IRBs); time and effort reporting; research involving animals and IACUCs; and personnel management.

2012 Faculty Workload Survey Research Report, Federal Demonstration Partnership, 2014
The Federal Demonstration Partnership (FDP) is a cooperative initiative among 10 federal agencies and 119 institutional recipients of federal funds, sponsored by the National Academies, with a purpose of reducing administrative burden associated with federal research grants and contracts. In 2012, the FDP conducted a survey of PIs of federally-funded projects to determine the impact of federal regulations and requirements on the research

process. In the survey, responses were obtained from 13,453 PIs from 111 FDP member institutions.

Findings of the FASEB Survey on Administrative Burden, 2013
FASEB represents 26 scientific societies and over 115,000 researchers. FASEB developed an online survey tool to solicit feedback on administrative burden.

See below for the specific key findings considered by the Working Group.

Working Group Analysis of Key Findings from Recent Reports, Communications, and Surveys on Reducing Administrative Burden to Researchers and Research Institutions

This table presents a condensed description of the key findings from the eight reports, communications, and surveys; the Working Group's analysis; and proposed actions. Where a key finding is similar or identical in different documents, it is listed once. The full text of the documents reviewed is available at https://olaw.nih.gov/21st-century-cures-act.htm.

Summary of Key Findings and Working Group Analysis	
1. Advisory Board: Key Findings • A group of experts, possibly a subcommittee of the Research Policy Board, should be appointed to serve as advisors during the review of regulations, policies, and guidance as mandated by the 21st Century Cures Act. • Current PHS and USDA regulations, policies, guidance, and FAQs should be reviewed by an external advisory committee to ensure they emphasize matters of core importance to animal welfare identified in statutory language.	**Advisory Board: Working Group Analysis and Proposed Actions** • Based on NIH OLAW's past use of RFIs concerning adoption of the 8th edition of the NAS *Guide*, implementation of the 2013 edition of the AVMA (American Veterinary Medical Association) Guidelines for the Euthanasia of Animals, and guidance regarding significant changes to ongoing animal activities, use of the RFI ensures broad input from interested stakeholders and is cost effective and efficient. • USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service. USDA will include a statement in its policy manual to explain that such polices are clarifications or interpretations of the Animal Welfare Act (AWA) and Animal Welfare Regulations, which are the only legally binding requirements. • The agencies do not support this approach as it is less transparent, would minimize the impact of input from the broader community, and would slow the process for stakeholder engagement. In addition, the rulemaking process under the Administrative

	Procedures Act already allows public and stakeholder input on proposed regulations before becoming a final rule.
2. Oversight: Key Findings • Consider consolidating all agency animal research oversight into a single agency. • Consider a single set of guidelines, perhaps modeled after the Common Rule used in human subjects research. • Amend the definition of animal in 7 U.S.C. § 2132 of the AWA to include all vertebrates to align USDA and NIH and harmonize US policy with other countries and industry standards. • Amend 7 U.S.C. § 2137 and § 2138 of the AWA to prohibit the use of random source dogs and cats in research. • Amend 7 U.S.C. § 2143 to require the use of alternative test methods and strategies whenever available. • Harmonize all NIH and USDA requirements on animal welfare to the highest possible standard.	**Oversight: Working Group Analysis and Proposed Actions** • The US government is organized with various agencies responsible for oversight of different functions based on various mandates, regulations, and guidelines, with overlapping areas of authority. NIH, USDA, and FDA cooperate to harmonize oversight of research animal subjects as described earlier in this report. NIH operates by authority of the Public Health Service (PHS) Act; USDA operates under the authority of the AWA; and FDA operates by authority of the Federal Food, Drug, and Cosmetic Act and the PHS Act. • The condition of human subjects used in research differs from the condition of animals and therefore requires different oversight and regulation. It is necessary to provide 24/7 husbandry, housing, and medical care for animals used in research as mandated by the AWA and the PHS Policy. • Amendments to 7 U.S.C. is outside the scope of the Working Group and would require Congressionally-initiated statutory changes.
3. Guidance: Key Findings • New rules should be considered requiring any proposed policy, guidance, or FAQ to have a 60-day comment period. • Agencies should avoid regulating through guidance. • USDA and OLAW could allay concerns by specifically stating when a practice is not required. • Agencies should refrain from modifying their regulations without consulting the regulated community.	**Guidance: Working Group Analysis and Proposed Actions** • NIH OLAW plans to allot a minimum of 60 days for comments to significant policy guidance. This will include any new interpretations of the PHS Policy, NAS *Guide*, or the AVMA Guidelines for the Euthanasia of Animals. Such guidance will focus on high risk animal welfare concerns affecting institutions. • NIH OLAW issues guidance as needed to: ○ clarify the meaning or language of policy, guidance, or regulation, as deemed necessary by NIH OLAW or in response to requests from the research community; ○ reduce administrative burden, especially to harmonize with other federal regulations and guidance; and ○ ensure compliance with federal laws, regulations, guidance, and Congressional and Executive directives.

	• NIH OLAW plans to review its disclaimer concerning current guidance to emphasize that "unless specific statutory or regulatory requirements are cited, the guidance should be viewed as recommendations in that an institution may use an alternative approach if the approach satisfies the requirements of the PHS Policy." • USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service. USDA will include a statement in its policy manual to explain that such polices are clarifications or interpretations of the AWA and the Animal Welfare Regulations, which are the only legally binding requirements.
4. PHS Policy, NAS *Guide*: Key Findings • Eliminate the PHS requirement for compliance with the NAS *Guide*. Use it as a best practices document. • "Should" statements in the NAS *Guide* should not be enforced as "must" statements.	**PHS Policy, NAS *Guide:* Working Group Analysis and Proposed Actions** NIH OLAW does not support this approach, as such a change would negatively impact animal welfare. Since the adoption of the PHS Policy in 1985, NIH has required that Assured institutions base their programs of animal care and use on the NAS *Guide*, a respected resource of best practices in the humane care and use of laboratory animals prepared by leading international subject matter experts. The PHS Policy IV.B.3. requires that: "The IACUC shall prepare reports of their semiannual program reviews and animal facility inspections and submit the reports to the Institutional Official (IO). The reports must contain a description of the nature and extent of the institution's adherence to the *Guide* and the PHS Policy, must identify specifically any departures from the provisions of the *Guide* and the PHS Policy, and must state the reasons for each departure." "Should" statements in the *Guide* are standards in animal care and use practiced universally by the biomedical research community to ensure animal welfare. Deviation from a "should" statement that is not described as an exception in the *Guide* or due to a performance standard must be reported to the IO. Risk aversion practices on the part of institutions contribute to burden from this requirement of the PHS Policy. There is flexibility with the use of performance standards, and NIH OLAW's guidance offers flexibility for

	professional judgment at the institution for "should" statements in the *Guide*.
5. PHS Policy, Protocol, and Grant Congruence: Key Findings Eliminate the requirement for protocol and grant congruency.	**PHS Policy, Protocol, and Grant Congruence: Working Group Analysis and Proposed Actions** PHS Policy and the NIH Grants Policy Statement (NIH GPS, chapter 4.1.1.2) require the institution to verify, before award, that the IACUC has reviewed and approved those components of grant applications and contract proposals related to the care and use of animals. This is not an explicit requirement for the IACUC to do a side-by-side comparison of an application or proposal and the IACUC protocol. However, institutions are responsible for ensuring that the information the IACUC reviews and approves is congruent with what is in the application or proposal. Grant-to-protocol congruency is required by NIH only at the first time of competitive award. Institutions are free to devise a workable mechanism to accomplish this end. One method to prevent inconsistencies between the information submitted to PHS and that on the IACUC protocol is to implement a procedure for direct comparison. Some institutions have delegated this responsibility to a particular office or position (e.g., sponsored programs or compliance office).
6. Protocol Review, Continuing Review: Key Findings • A risk-based process similar to human subject review should be established. • USDA annual and NIH triennial reviews should be harmonized into a continuing review process without compromising animal welfare. • Harmonize regulatory requirements for IACUC approval across the funding agencies.	**Protocol Review, Continuing Review: Working Group Analysis and Proposed Actions** • According to Title 9 Chapter 1 Section 2.31(d), in order for the IACUC to approve proposed activities or proposed significant changes to ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with this subchapter unless acceptable justification for a departure is present in writing. Also, 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. • USDA will propose, through notice and comment rulemaking, a regulatory change to Title 9 Chapter 1, Subchapter A-Animal Welfare, Section 2.31(d)(5), to remove the requirement that IACUCs conduct "continuing reviews of activities covered by [the Animal

	Welfare Act] at appropriate intervals . . . but not less than annually," and, instead, insert a requirement that IACUCs conduct a three-year *de novo* review of activities. IACUCs would continue to review, approve, require modification to, or withhold approval of significant changes regarding the care and use of animals in ongoing activities, as required by 9 CFR §§ 2.31(d)(7), 2.31(e).
7. Protocol Review, Expedited Review: Key Findings • Institutions should use Designated Member Review rather than a full IACUC review for applicable (low-risk) protocols and protocol modification. • Agencies should create exempt and expedited review categories similar to human subjects regulations. • Allow small changes to protocols to be approved through a simplified administrative process. • OLAW could amend its guidance documents on review of modifications and amendments to permit more rapid turnaround. • Protocol review and approval time is too long; research can be delayed by months waiting for minor modifications to animal use protocols. • Encourage IACUCs to use DMR instead of FCR for protocol amendments that do not significantly affect animal welfare. • Agencies should allow changes to the exact number of animals required for a grant to be approved through a simplified administrative process or rely on reporting of animal use.	**Protocol Review, Expedited Review: Working Group Analysis and Proposed Actions** NIH OLAW, in coordination with USDA, plan to review and develop resources to support IACUCs' use of existing options that streamline protocol review and significant changes to approved protocols without compromising animal welfare.
8. Protocol Review, *de novo* Review: Key Findings • The PHS requirement for a re-review of animal-use protocols every three years should be changed to five years to better match grant length.	**Protocol Review, *de novo* Review: Working Group Analysis and Proposed Actions** • Extending the period of approval is a risk to animal welfare, as investigators are not able to describe their proposed animal experiments in the detail required for adequate IACUC review and approval for the entire five years of a grant. Protocols are frequently amended during the three-year approval period to accommodate

• Encourage federal agencies to clarify that animal care and use protocols do not need to be completely rewritten to satisfy the requirements for annual or triennial re-review.	changes in experimental design. Performing work not described in a protocol is the most frequently occurring noncompliance reported to NIH OLAW with the current three-year renewal requirement. Extending the period to five years would exacerbate the risk of noncompliance. In addition, grants have different award periods (not all are five years) and there are no requirements for one to one match of protocol to grant. Matching protocol approval to a grant approval decreases the flexibility that institutions currently have with a single protocol covering multiple grants or vice versa. • NIH OLAW, in coordination with USDA, plan to review and develop resources to support IACUCs' use of existing options that streamline protocol review and significant changes to approved protocols without compromise to animal welfare. • According to Title 9 Chapter 1 Section 2.31(d), in order for the IACUC to approve proposed activities or proposed significant changes to ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with this subchapter unless acceptable justification for a departure is present in writing. Also, 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. • USDA will propose, through notice and comment rulemaking, a regulatory change to Title 9 Chapter 1, Subchapter A-Animal Welfare, Section 2.31(d)(5), to remove the requirement that IACUCs conduct "continuing reviews of activities covered by [the Animal Welfare Act] at appropriate intervals . . . but not less than annually," and, instead, insert a requirement that IACUCs conduct a three-year *de novo* review of activities. IACUCs would continue to review, approve, require modification to, or withhold approval of significant changes regarding the care and use of animals in ongoing activities, as required by 9 CFR §§ 2.31(d)(7), 2.31(e).

9. Protocol Review, USDA Policy #12: Key Findings

Amend the language of USDA Policy #12 for literature searches to be consistent with the AWA and Animal Welfare Regulations.

Protocol Review, USDA Policy #12: Working Group Analysis and Proposed Actions

- In Section 2143 of the AWA, the Secretary shall promulgate standards to govern the humane handling, care, treatment, and transportation of animals by dealers, research facilities, and exhibitors. With respect to animals in research facilities, the standards include requirements that the principal investigator consider alternatives to any procedure likely to produce pain to or distress in an experimental animal. In Title 9 Chapter 1 Section 2.31(d), the IACUC shall determine that the proposed activities or proposed significant changes to ongoing activities entail a consideration by principal investigator of alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and the provision of a written narrative description of the methods and sources, e.g., the Animal Welfare Information Center, was used to determine that alternatives were not available.
- The Animal Care policy manual was established in 1997 and revised in 2011. The purpose of the manual was to provide guidance to USDA Animal Care field inspectors and members of the AWA-regulated community on how certain provisions of the Animal Welfare regulations should be interpreted. Policy #12 provided guidance to investigators on the consideration of alternatives to painful and distressful procedures and information for the narrative of methods used and sources consulted to determine the availability of alternatives, including refinements, reductions, and replacements. The policy manual was removed from the USDA website in July 2018, and the policies are inoperative, while USDA conducts a review to ensure conformity with the AWA and Animal Welfare Regulations; harmonize with NIH OLAW guidance; and reduce investigator burden where possible. USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service.

10. Protocol review, USDA Policy #14: Key Findings USDA Policy #14 should be modified to allow multiple operative procedures at the discretion of the IACUC.	**Protocol Review, USDA Policy #14: Working Group Analysis and Proposed Actions** • Under Title 9 CFR, Section 2.31(d), the IACUC shall determine that the proposed activities or significant changes in ongoing activities meet the following requirements, that no animal will be used in more than one major operative procedure from which it is allowed to recover, unless: justified for scientific reasons by the principal investigator, in writing; required as a routine veterinary procedure or to protect the health and wellbeing of the animal as determined by the attending veterinarian; or in other special circumstances as determined by the Administrator on an individual basis. • The Animal Care policy manual was established in 1997 and revised in 2011 to provide guidance for USDA Animal Care field inspectors, and owners and handlers of animals subject to the AWA, stating how certain provisions of the Animal Welfare regulations should be interpreted. Policy #14 provided guidance to investigators on the use of surgically-altered animals received from a dealer and subsequently used in a major operative procedure. It also provided clarification of the exemptions due to special circumstances provided in the AWA and Animal Welfare Regulations. The policy manual was removed from the USDA website in July 2018, and the policies are inoperative, while USDA conducts a review to ensure conformity with the AWA and Animal Welfare Regulations; harmonize with NIH OLAW guidance; and reduce investigator burden where possible. USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service.
11. Semiannual Inspection: Key Findings • Congress should amend the AWA, Health Research Extension Act, and PHS Policy requirements for semiannual inspection and program review to at least annual inspection and program review. • Agents of the IACUC should be able to conduct the inspections.	**Semiannual Inspection: Working Group Analysis and Proposed Actions** • NIH OLAW and USDA do not support this approach as it would negatively impact animal welfare. As described in the NAS *Guide*, the responsibility of the IACUC is to oversee and routinely evaluate the program of animal care and use (*Guide* page 24). Both the Health Research Extension Act and the AWA require the IACUC to inspect

• USDA should allow for risk-based inspections. • Reduce or consolidate overlapping inspections by agencies and accreditors. • Reduce multiple, uncoordinated inspections per year that disrupt research.	animal care and use facilities, including sites used for animal surgeries, every six months. A change in the frequency of IACUC inspections would require statutory changes to both laws. The PHS Policy allows flexibility in how and by whom the inspections are conducted. • Section 2143(b)(3) of the AWA requires the IACUC to inspect at least semiannually all animal study areas and animal facilities of such research facility, and review as part of the inspection –(A) practices involving pain to animals, and (B) the condition of animals, to ensure compliance with the provisions of this chapter to minimize pain and distress to animals. Exceptions to the requirement of inspection of such study areas may be made if animals are studied in their natural environment and the study area is prohibitive to easy access. USDA allows flexibility in how and by whom the inspections are conducted. • NIH OLAW, in coordination with USDA, plan to develop guidance to address existing flexibilities.
12. Noncompliance and Reporting: Key Findings • NIH guidance on prompt reporting of noncompliance should only include incidents that jeopardize the health or wellbeing of animals. • The current guidance for reporting a serious or continuing noncompliance with the PHS Policy or a serious deviation from the provisions of the NAS *Guide* should be revised. Currently the guidance does not distinguish between the two types of reportable incidents in terms of the requirements for reporting or the examples of what should be promptly reported. Since the PHS Policy specifically addresses the functions of the IACUC, including the review of proposed research activities and the institutional requirements for maintaining required records, any failure to comply with any of the requirements delineated in these sections of the PHS Policy should be promptly reported. When it comes to deviations from the provisions of the NAS *Guide*, the requirement for prompt reporting should be based upon whether the incident had a negative impact on animal health and wellbeing, while any incidents that did not directly impact animal health and wellbeing could be	**Noncompliance and Reporting: Working Group Analysis and Proposed Actions** • The PHS Policy, section IV.F.3., requires that: "The IACUC, through the Institutional Official, shall promptly provide OLAW with a full explanation of the circumstances and actions taken with respect to: 1) any serious or continuing noncompliance with this Policy; 2) any serious deviation from the provisions of the *Guide*; or 3) any suspension of an activity by the IACUC." All institutions with Animal Welfare Assurances (Assurance) are required to comply with the PHS Policy. NIH OLAW plans to review the guidance in NIH Guide Notice NOT-OD-05-034 on reporting requirements to refine and update examples of reportable situations, examples of situations not normally reported, the timeframe for reporting, and the information to be reported. • Animal Care has instituted a process to incentivize registrants to self-identify, self-correct, and voluntarily report serious noncompliance. This will affect how and when facilities are cited for serious noncompliance. The incentives encourage facilities to proactively

summarized in the annual report. In addition, the level of detail required in the report should be changed so that the report addresses the general nature of the incidents and how the incident was addressed. • Agencies should adjust their requirements for reporting so that animal-related noncompliance reports are tiered to the level or significance of impact on animals and included in an annual report rather than submitted on an individual event basis. • The NIH should revamp animal care compliance regulations to the minimum required for safe animal use.	self-identify areas of noncompliance and take swift action. Non-critical noncompliance will not be cited on inspection reports if the facility discovers the noncompliance on its own and immediately take appropriate correct action to establish measure to prevent reoccurrence. Critical noncompliance will not be cited on the report if the facility discovered the noncompliance on its own in a timely manner, took immediate and appropriate corrective action and established measures to prevent recurrence, had no repeat or critical noncompliance at that site in the last 12 months, and has not had a critical noncompliance in the same section and subsection of the regulations within the last 24 months at the same site.
13. Annual Reports: Key Findings • Reporting, Assurances, and verifications to agencies should be reduced and streamlined. Annual reports to individual agencies about animal care programs should be replaced by a single annual report under the proposed Federal-wide Assurance mechanism. Processes that are redundant to the IACUC approval process, such as the Vertebrate Animals section of PHS grant applications and the Department of Defense central administrative protocol review, should be eliminated. • USDA should modify the Animal Welfare Regulations and annual report to require prospective counts of animals in procedures likely to cause pain or distress.	**Annual Reports: Working Group Analysis and Proposed Actions** • Syncing the reporting period and due date for USDA and NIH OLAW reports will minimize time devoted to collection of reporting data. IACUCs and investigators will be less burdened with administrative actions and able to attend to their animal welfare and research responsibilities. • Title 9 CFR Section 2.36 states the annual report shall: (1) Assure that professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by the research facility; (2) Assure that each principal investigator has considered alternatives to painful procedures; (3) Assure that the facility is adhering to the standards and regulations under the Act, and that it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the IACUC. A summary of all such exceptions must be attached to the facility's annual report. In addition to identifying the IACUC-approved exceptions, this summary must include a brief explanation of the exceptions, as well as the species and number of animals affected. The report is to also list the animals held by a facility but not used in any research that year; animals used in research; no pain involved; no pain drugs administered; animals used in research; pain involved; pain drugs

	administered; and animals used in research; pain involved; no pain drugs administered. • The animals listed under the different pain and distress categories may be retrospective or prospective. Retrospective reporting involves collecting data on individual animals to put each study animal into the most appropriate category based on clinical signs of pain and distress. While more labor intensive, this method generally produces more accurate reporting. Prospective reporting means that all animals used for a particular activity may be categorized in the highest applicable pain category. This method is less labor intensive but may result in over-reporting. If animals experience pain or distress during the study due to research procedures that are in a higher pain category than originally designated, the animal(s) are to be reported on the annual report in the higher pain category. The reporting will be retrospective to indicate the pain or distress level the animal actually experienced.
14. Standard Operating Procedures: Key Findings • Recommend that federal agencies collaborate with research institutions as well as organizations representing investigators and institutions to identify and disseminate model programs and best practices (e.g., for financial management and Institutional Review Board / IACUC review) that could be adapted for use at other institutions. • Develop standard operating procedures and a single set of guidelines that can be cited on IACUC protocols. • For approved animal disease models, the protocols for induction of disease, monitoring, and analgesia should be available and easily imported into other protocols. • Provide standard acceptable protocols and drug dosage ranges for commonly used drugs. • Develop standard operating procedures for common experimental procedures that can be cited within an IACUC application.	**Standard Operating Procedures: Working Group Analysis and Proposed Actions** NIH OLAW, in coordination with USDA, will continue to support the efforts of the FDP members to create the CUSP as a repository of best practices for standard procedures used for research involving animals. IACUCs have the option to integrate CUSP into their institutional processes to reduce burden on investigators. Use of CUSP would be optional and open-access.

15. Standard Protocol: Key Findings	**Standard Protocol: Working Group Analysis and Proposed Actions**
Reduce IACUC requirements for experimental details that are unrelated to evaluating the health and safety of the animals being used.	NIH OLAW and USDA support a flexible approach to foster good science while ensuring animal welfare. NIH OLAW will consider updates to simplify its sample animal study protocol form and pilot the revised protocol form through FDP.
16. Training: Key Findings	**Training: Working Group Analysis and Proposed Actions**
• Training requirements should be tailored to an individual's job responsibilities. • Create an online comprehensive training resource to provide a uniform core curriculum for basic laboratory safety, human subjects protections, and care and use of laboratory animals. • Centralize tracking for completion of basic training modules that is readily accessible by individual investigators, institutional staff, and agency administrators.	• NIH OLAW, in coordination with USDA, will continue to support the development of industry-led training and resources to assist institutional leadership, IACUC members, and IACUC administrators in reducing the burden on investigators. • Title 9 CFR Section 2.32(a) states It is the responsibility of the research facility to ensure that all scientists, research technicians, animal technicians, and other personnel involved in animal care, treatment, and use are qualified to perform their duties.
17. Burden: Key Findings	**Burden: Working Group Analysis and Proposed Actions**
PIs estimated that an average of 42% of their research time was spent on meeting requirements rather than conducting active research.	NIH OLAW, in coordination with USDA, will continue to support the development of industry-led training and resources to assist institutional leadership, IACUC members, and IACUC administrators in reducing burden on investigators.
18. NIH Grants Policy: Key Findings	**NIH Grants Policy: Working Group Analysis and Proposed Actions**
• NIH Grants Policy should be modified to factor in risk to animals concerning the change of scope of an award. • Adopt a streamlined approach in which one IACUC approval satisfies all institutions funded by the same grant. • Delineate responsibilities between scientific review groups and IACUCs regarding the review of the vertebrate animal section of grants and the animal use protocol to avoid duplication of effort.	• NIH Grants Policy allows the PI to make changes to many aspects of a funded-project's objectives without prior approval from NIH. Exceptions that require prior approval from the NIH grants management officer include substitution of one animal model for another or change from the approved use of live animals. If in doubt about whether prior approval is required, the PI should contact the grants management officer for the award. • NIH and USDA agree that review of a research project or evaluation of a program or facility by more than one recognized IACUC is not a federal requirement. IACUCs may choose which IACUC will review protocols for the animal activities being conducted. NIH Grants

Policy Statement on Written Agreements (NIH GPS, chapter 15.2.1) requires that awardees have a formal written agreement with consortium participants that addresses the negotiated scientific, administrative, financial, and reporting requirements of the grant. This written agreement must incorporate applicable public policy requirements, including agreement for meeting the PHS Policy (IV.B.2.) requirement for review and approval of proposed animal activities, significant changes to animal activities, and semiannual facilities review by an IACUC.

- Review of proposed activities by a Scientific Review Group (SRG), also known as a study section, is required by the NIH Grants Policy Statement (Part I., 2.4 The Peer Review Process) and federal law (sections 406 and 492 of the Public Health Service Act, as amended by the NIH Reform Act of 2006). If the proposed research includes the use of animal subjects, review of the Vertebrate Animals Section (VAS) and proposed animal experiments is conducted by the SRG. After determination of an award, but before release of funds, IACUC review and approval ensure compliance with the PHS Policy and the institution's Assurance. Compliance with PHS Policy is a term and condition of the NIH Grants Policy Statement (Part II, Subpart A 4.1.1 Animal Welfare Requirements) to obtain PHS funds. In 2016 NIH revised the grant application to remove redundancy with IACUC review while meeting the requirements of the PHS Policy. The changes simplify the VAS criteria and reduce burden on applicants and reviewers. The justification for the number of animals is no longer required in the VAS and is instead an element of rigor in the experimental design, described in the Research Strategy section of the application, and considered during SRG review. Because the IACUC review does not coincide with an awarded grant application, the review must consider the rationale for the approximate number of animals to be used and that the number proposed is necessary to obtain valid results as required by PHS Policy.

19. PHS Assurance: Key Findings	PHS Assurance: Working Group Analysis and Proposed Actions
Streamline the NIH Assurance to a short online form similar to that for human subjects.	The condition of human subjects used in research differs from the condition of animals and therefore requires different oversight and regulation. The PHS Policy is explicit about the required elements in the Assurance to provide oversight of animal welfare for PHS-funded activities.
20. AWA Regulations: Key Findings	**AWA Regulations: Working Group Analysis and Proposed Actions**
Regulations should state what is required to ensure uniform implementation and reduce confusion caused by ambiguity.	The AWA is a statute (Public Law 89-544, USC 7 § 2131-2159) enacted by Congress in 1966 that established the expectation that humane care and treatment will be provided for certain animals that are used for research, exhibited to the public, sold commercially as pets, and transported in commerce. The provisions in the AWA are implemented through the Animal Welfare Regulations (Code of Federal Regulations, Title 9, Chapter 1, Subchapter A-Animal Welfare). The regulations are developed with public input and contain performance-based approaches to animal welfare which allow flexibility. USDA is revising its guidance documents to reduce ambiguity and confusion.

Appendix 2. Analysis of Responses to the Request for Information

Working Group Analysis of the Responses to the Request for Information (RFI) Concerning Proposed Agency Actions

This table presents a summary of the public responses received to RFI topics A1 to A5 and B1 to B6, the Working Group's analysis, and proposed actions. Due to the volume of responses received, similar comments were combined for brevity and efficiency and edited for clarity. Comments that were not responsive to topics presented in the RFI are not included.

Public input was sought on:

A. Proposed actions that the agencies are considering. (Topics A1 to A5)
B. Whether certain tools and resources are or would be helpful for reducing burden on investigators. (Topics B1 to B6)

A1: Allow investigators to submit protocols for continuing review using a risk-based methodology		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments on why agencies should adopt A1. Adoption of risk-based methodologies would: • result in decreased burden for researchers and IACUCs without degrading protections for the animals • allow more time for high-risk research review • allow more time for science Public comments on how agencies should adopt A1. • include streamlined paths for review and approval of low-risk, non-invasive, or minimally invasive animal activities • allow single member review (without approval by committee as in DMR) • allow administrative review for low risk procedures	Public comments on why agencies should not adopt A1. Animal welfare reasons: • proposed action would further loosen protocol review rules and expedite the approval of animal use that is not *unavoidable for the conduct of scientifically valuable research* (9 CFR § 2.31(e)(4)) • protocols that do not involve invasive procedures may still cause harm to animals; animals are injured or die during routine laboratory practices • animal welfare violations can occur in low risk activities • without review, new methods and 3Rs may not be applied	• USDA will propose, through notice and comment rulemaking, a regulatory change to Title 9, Chapter 1, Subchapter A-Animal Welfare, Section 2.31(d)(5), to remove the requirement that IACUCs conduct "continuing reviews of activities covered by [the Animal Welfare Act] at appropriate intervals . . . but not less than annually," and, instead, insert a requirement that IACUCs conduct a three-year *de novo* review of activities. IACUCs would continue to review, approve, require modification to, or withhold approval of significant changes regarding the care and use of animals in ongoing activities, as required by 9 CFR §§ 2.31(d)(7), 2.31(e). The regulatory change brings alignment between USDA and NIH requirements and reduces the time and effort dedicated to reviewing protocols on an annual basis, while retaining the

• define low-risk as non- or minimally invasive, humane euthanasia, USDA pain category B or C research, genotyping, low pain or distress • use standard protocols for breeding, euthanasia, and tissue harvest • procedures in standard use should be considered low risk and could be check-box format on protocol form • risk-based process amendment could be modeled on NIH significant changes NOT-OD-14-126 with administrators conducting low risk approvals • extend PHS Policy footnote eight to include letting IACUC determine the best method for overseeing approved animal use activities (IACUC determines risk-based approach) • couple with post-approval monitoring program • if a researcher reports unexpected injuries or mortalities full review is warranted	Risk assessment reasons: • risk assessments vary widely and are too subjective • implementation of risk-based weakens monitoring, puts animals at risk, and undermines animal protection • PIs misjudge pain categories, indicating they are not the best choice to determine risk • determination of risk should be made by or in consultation with experts (e.g., roundtables, consensus literature review by experts), not by oversight agencies Policy and or legal reasons: • circumvention of review process contradicts the intent of the 1985 AWA amendments: *A quorum shall be required for all formal actions of the [IACUC]* • Existing policies permitting DMR and DMR subsequent to FCR are effective for low-risk research; change is not needed Administrative burden reasons: • change to rules will increase institution drive to additional self-imposed burden	benefits of a thorough *de novo* review every three years and ongoing review of any significant changes. The IACUC may choose to review a protocol at an interval more frequently than three years as part of conducting a program review. • NIH OLAW and FDA support USDA's proposed change.
Apply human subjects regulatory framework to research animals / Common Rule	Application of the Common Rule is inappropriate because protections of human and animal subjects are different with respect to voluntary consent and choice. Animals are vulnerable populations that require additional protections	The condition of human subjects used in research differs from the condition of animals and therefore requires different oversight and regulation. It is necessary to provide 24/7 husbandry, housing, and medical care for animals used in research, whether the research is invasive, minimally invasive, or noninvasive, as mandated by the AWA and the Public Health Service Act. Some work with animals is exempt

	from IACUC oversight, including observational wildlife studies, use of materials (e.g., blood, tissues) that are collected for another purpose (e.g., clinical needs, organs from slaughterhouse). The agencies plan to provide updated resources on what is exempt from IACUC review.
Permit repeated surgeries and procedures after a specified time period to reduce the number of animals at the discretion of IACUC	• Under Title 9 CFR Section 2.31(d), the IACUC shall determine that the proposed activities or significant changes in ongoing activities meet the following requirements, that no animal will be used in more than one major operative procedure from which it is allowed to recover, unless: justified for scientific reasons by the principal investigator, in writing; required as a routine veterinary procedure or to protect the health and wellbeing of the animal as determined by the attending veterinarian; or in other special circumstances as determined by the Administrator on an individual basis. • The Animal Care policy manual was established in 1997 and revised in 2011 to provide guidance for USDA Animal Care field inspectors, and owners and handlers of animals subject to the AWA, stating how certain provisions of the Animal Welfare regulations should be interpreted. Policy #14 provided guidance to investigators on the use of surgically-altered animals received from a dealer and subsequently used in a major operative procedure. It also provided clarification of the exemptions due to special circumstances provided in

		the AWA and Animal Welfare Regulations. The policy manual was removed from the USDA website in July 2018, and the policies are inoperative, while USDA conducts a review to ensure conformity with the AWA and Animal Welfare Regulations; harmonize with NIH OLAW guidance; and reduce investigator burden where possible. USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service.
Reduce frequency of review and approval of some research: • three-year period for review of low-risk research • five-year period for review of all research (new, continuing, *de novo*, annual)	• Continuing review provides opportunity for PI, IACUC, and staff training • Benefit of continuing review would be lost: ○ updates the IACUC of project status ○ ensures continuing compliance with standards ○ re-evaluation of animal activities at appropriate intervals	• DMR offers an expeditious turnaround for three-year *de novo* review. • DMR may be considered for review of research activities determined by the IACUC to be of low risk. The agencies plan to issue updated resources to encourage the use of DMR for low-risk activities. • PHS Policy requires that a complete review be conducted; it does not require that the protocol be rewritten. IACUCs may review the initial protocol and all modifications to reduce administrative burden on investigators. • Extending the period of approval is a risk to animal welfare, as investigators are not able to predict sufficiently to describe their proposed animal experiments in the detail required for adequate IACUC review and approval for the entire five years of a grant. Protocols are frequently amended during the three-year approval period to

		accommodate changes in experimental design. Performing work not described in a protocol is the most frequently occurring noncompliance reported to NIH OLAW with the current three-year renewal requirement. Extending the period to five years would exacerbate the risk of noncompliance. • Science is fluid and protocols can be rewritten and amended as needed throughout the approval period. Grants have different award periods (not all are five years) and there are no requirements for a one-to-one match of protocol to grant. Matching protocol approval to a grant approval decreases the flexibility that institutions currently have with a single protocol covering multiple grants or vice versa.

A2: Allow annual reporting to OLAW and USDA on the same reporting schedule and as a single report through a shared portal		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments on why agencies should adopt A2. A single portal and reporting schedule would: • reduce confusion and errors • ensure reports to both agencies are congruent • encourage accuracy • maximize transparency, accountability, and animal welfare	Public comments on why agencies should not adopt A2. A single portal and reporting schedule would: • not improve animal welfare • not reduce burden on the investigator; • instead, reduce the requirements for noncompliance reporting to OLAW to only when animal welfare is impacted • a single report would enable intentional violations to be unreported and human error uncorrected	• The intent of this proposed change is to improve coordination of regulations and policies concerning annual reporting. Syncing the reporting period and due date for USDA and NIH OLAW reports will minimize time devoted to the collection of reporting data. IACUCs and investigators will be less burdened with administrative actions and able to attend to their animal welfare and research responsibilities. • Title 9 CFR Section 2.36 states the annual report shall: (1) Assure that professionally

- instead, convene agencies and researchers to assess feasibility of a single oversight agency
- AAALAC report should also be included

acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by the research facility; (2) Assure that each PI has considered alternatives to painful procedures; (3) Assure that the facility is adhering to the standards and regulations under the Act, and that it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the IACUC. A summary of all such exceptions must be attached to the facility's annual report. In addition to identifying the IACUC-approved exceptions, this summary must include a brief explanation of the exceptions, as well as the species and number of animals affected. The report is to also list the animals held by a facility but not used in any research that year; animals used in research, no pain involved, no pain drugs administered; animals used in research, pain involved, pain drugs administered; and animals used in research, pain involved, no pain drugs administered.

- The animals listed under the different pain and distress categories may be retrospective or prospective. Retrospective reporting involves collecting data on individual animals to put each study animal into the most appropriate category based on clinical signs of pain and distress. While

	more labor intensive, this method generally produces more accurate reporting. Prospective reporting means that all animals used for a particular activity may be categorized in the highest applicable pain category. This method is less labor intensive but may result in over-reporting. If animals experience pain or distress during the study due to research procedures that are in a higher pain category than originally designated, the animal(s) are to be reported on the annual report in the higher pain category. The reporting will be retrospective to indicate the pain or distress level the animal actually experienced.
Public comments on how agencies should adopt A2. • streamline data required for submission • establish a single template • information submitted through a single portal should generate separate reports, providing only information relevant to that agency's requirements • information should be made publicly available by e-posting and FOIA • information should not be made publicly available; USDA should harmonize to OLAW policy of not e-posting • harmonize so USDA includes all vertebrates • add checkboxes to OLAW's report • generalized information should be used so the report could be compiled, without seeking input from investigators, using only information on-file in the IACUC office	• USDA and NIH OLAW plan to review the reporting elements and simplify where possible, but keep the reports separate and explore the development of a single reporting portal. • USDA recently developed an online portal for submitting annual reports. USDA included the research community in the planning and development of the system. An online annual reporting system will streamline data submission. • USDA intends to pursue a regulatory change to Title 9 CFR Section 2.30(a)(1) to eliminate the need to renew the registration every three years. The annual report will be updated to contain sufficient information to update USDA records, and no further

- eliminate USDA animal numbers reporting
- eliminate average daily census report

information regarding the registration would be required.

A3: Harmonize the guidance from NIH and USDA to reduce duplicative considerations of alternatives to painful and distressful procedures		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments on why agencies should adopt A3. • it would enable consistent assessment of research animal welfare • investigators need clear, concise guidelines Public comments on how agencies should adopt A3. • harmonizing without reducing any requirements by defaulting to the highest standard • blending duplicative considerations • harmonizing NAS *Guide* and USDA regulations • conforming existing federal requirements for species currently covered by USDA and those by the PHS Policy to the least burdensome standard • eliminating database and keyword searches; instead, have researchers verify the consideration of alternatives and provide a written description of the methods and sources used to determine that alternatives were not available • developing forms to validate the implementation of 3Rs • requiring submissions be evidence-based and providing updated guidance on a regular basis to ensure best practices	Public comments on why agencies should not adopt A3. • researchers should spend more time conducting searches for and implementing less painful and distressful procedures • alternatives are still progressing • alternatives are more relevant and predictive of human health • protecting animal welfare is never a burden • federal agencies should promote development of alternatives Eliminate consideration of alternatives because: • 3Rs should be validated in protocols rather than by literature searches • it is difficult to design a search that seeks the absence of results • literature searches rarely yield usable alternatives • pro-forma literature search does not minimize pain and distress; permit investigators to concentrate on making the research justification clear and reviewed by IACUC	• The agencies plan to review and enhance current resources to support IACUCs' use of existing options that streamline protocol review and significant changes to approved protocols, including the use of the vertebrate animal section in the grant proposal. • In Section 2143 of the Animal Welfare Act, the Secretary shall promulgate standards to govern the humane handling, care, treatment, and transportation of animals by dealers, research facilities, and exhibitors. With respect to animals in research facilities, the standards include requirements that the principal investigator considers alternatives to any procedure likely to produce pain to or distress in an experimental animal. In Title 9 CFR Section 2.31(d), the IACUC shall determine that the proposed activities or significant changes in ongoing activities include that the principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources, e.g., the Animal Welfare Information Center, used to determine that alternatives were not available.

Other comments regarding alternatives to painful and distressful procedures: • revise Policy #12 to be consistent with and limited to Section 2.31(d)(1)(ii) • establish a consolidated resource for training, research, education, and outreach, like the National Centre for the Replacement, Refinement & Reduction of Animals in Research		• The Animal Care policy manual was established in 1997 and revised in 2011 to provide guidance for USDA Animal Care field inspectors and owners and handlers of animals subject to the AWA, stating how certain provisions of the Animal Welfare regulations should be interpreted. Policy #12 provided guidance to investigators on the consideration of alternatives to painful and distressful procedures and information for the narrative of methods used and sources consulted to determine the availability of alternatives, including refinements, reductions, and replacements. The policy manual was removed from the USDA website in July 2018, and the policies are inoperative, while USDA conducts a review to ensure conformity with the AWA and Animal Welfare Regulations; harmonize with NIH OLAW guidance; and reduce investigator burden where possible. USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service.
A4: Provide a minimum 60-day comment period for new OLAW policy guidance		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments supporting a public comment period for new OLAW policy guidance. • publicize the policy for comments and publicize why the final decision was made before implementation		• NIH OLAW plans to give a minimum of 60 days for comments to significant policy guidance. This will include any new interpretations of the PHS Policy, the NAS

• use a standard means to publicize guidance; do not publicize policy guidance through other means (e.g., Lab Animal, Q&A)
• seek comments on previous guidance that was provided without a comment period
• guidance documents should clearly state that they do not carry legal or regulatory force
• guidance documents should not be accompanied by a requirement to obtain agency approval for alternative methods or processes
• suggested duration of public comment period ranged from 3 days to 365 days
		Guide, or the AVMA Guidelines for the Euthanasia of Animals.
		• Such guidance will focus on high risk animal welfare concerns affecting institutions.
		• NIH OLAW issues guidance as needed to:
		  ○ clarify the meaning or language of policy, guidance, or regulation, as deemed necessary by NIH OLAW or in response to requests from the research community;
		  ○ reduce regulatory burden, especially to harmonize with other federal regulations and guidance; and
		  ○ ensure compliance with federal laws, regulations, guidance, and Congressional and Executive directives.
		• NIH OLAW plans to review its disclaimer concerning current guidance to emphasize that "unless specific statutory or regulatory requirements are cited, the guidance should be viewed as recommendations in that an institution may use an alternative approach if the approach satisfies the requirements of the PHS Policy."

Public comments about how to enact a public comment period for new OLAW guidance: • disperse information regarding proposed policy changes and how to submit comments widely among stakeholders; note that all taxpayers are stakeholders in federally funded research		Based on NIH OLAW's past success with RFIs concerning adoption of the 8th edition of the NAS *Guide*, implementation of the 2013 edition of the AVMA Guidelines for the Euthanasia of Animals, and the guidance regarding significant changes to ongoing animal activities, this method of receiving broad input from

• have near-final documents reviewed by an external advisory committee of experts from the regulated animal research community before they are disseminated for public comment or final agency review • circumventing rulemaking by issuing guidance is unacceptable • establish a Research Policy Board to review new policy guidance	interested stakeholders is cost-effective and efficient.

A5: Other approaches not previously mentioned* ***Because of the open-ended nature of this topic, the RFI responses have been grouped by broad topic areas or agency-specific topics where applicable**	
Government-wide Topics	**Working Group Analysis and Proposed Actions**
The policy on non-pharmaceutical grade compounds should be rewritten to reduce regulatory burden since most compounds in research are not available as pharmaceutical grade.	• NIH OLAW plans to review and update the guidance on non-pharmaceutical grade compounds to clarify the options for IACUC review. • The USDA Animal Care policy manual was established in 1997 and revised in 2011. The purpose of the manual was to provide guidance to USDA Animal Care field inspectors and members of the AWA regulated community on how certain provisions of the Animal Welfare regulations should be interpreted. Policy #3 provided guidance to investigators on the use of non-pharmaceutical grade substances. The policy manual was removed from the USDA website in July 2018, and the policies are inoperative, while USDA conducts a review to ensure conformity with the AWA and Animal Welfare Regulations; harmonize with NIH OLAW guidance; and reduce investigator burden where possible. USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service.
Agencies should form external advisory groups of experts involved in federally funded research to serve as advisors. The advisory group should include those involved with oversight responsibility at the	The agencies do not support this approach as it is less transparent, would minimize the impact of input from the broader community, and would slow the process for stakeholder engagement. In addition, the

institutional level, such as institutional administrators, IACUC members, veterinarians, and investigators engaged in animal research. This will foster progress and impartiality in the conduct of this review, which should take into account relevant regulations, policies, and guidance, along with the recommendations of this and other reports that have addressed regulatory burden associated with animal research	rulemaking process under the Administrative Procedures Act already allows public and stakeholder input on proposed regulations before becoming a final rule.
Recommend a Memorandum of Understanding (MOU) be established on animal care between FDA, NIH, USDA, and EPA. There is a MOU between EPA and FDA (FDA EPA IAG/MOU 224-78-8006), and a MOU between FDA, NIH, and USDA (MOU 225-16-010, APHIS Agreement No. 11-6100-0027-MU). Why not close the loop and have all agencies work collectively on addressing laboratory welfare in one agreement?	This request is beyond the scope of this working group. Representatives from all agencies (e.g., FDA, EPA, NIH, and USDA) work collaboratively in the interest of animal welfare. The MOU between EPA and FDA (EPA IAG/MOU 224-78-8006) is now expired and has been replaced with MOU 225-14-022. MOU 225-16-010 encompasses procedures for effective and efficient information sharing.
To continue to subject biomedical research to oversight by two separate federal agencies, no matter how convergent their regulations and interpretations may eventually become, will remain an unnecessary and unaffordable burden. Therefore, Congress and the Administration should relieve the US biomedical research community of this burden by consolidating laboratory animal oversight under the AWA. USDA has more than 50 years of experience in enforcing the AWA; resultant regulations and policies are well known by registered research institutions of all kinds and, just as importantly, are consistent and predictable. Coverage of most rats and mice, and all birds and other non-mammal vertebrates, which comprise the vast majority of animals used in the US, remains a gap in oversight. This gap should be closed by amending the AWA to eliminate these exemptions so all vertebrates used in research and testing are covered, regardless of species, category of institution involved (i.e., academia or industry), or source of funding.	This suggested approach is outside the scope of the Working Group and would require statutory changes.
USDA-specific Topics	**Working Group Analysis and Proposed Actions**
Have the AWA demand expertise of all members of the local Animal Care units.	This request is beyond the scope of the Working Group to reduce administrative burden for investigators.
Make the ACUCs a normal part of the committee system institutions and elect its members from active researchers.	This request is beyond the scope of the Working Group to reduce administrative burden for investigators.

Mandate use of the institutional legal system and state laws to deal with AWA allegations.	This request is beyond the scope of the Working Group to reduce administrative burden for investigators. However, the AWA Section 2145(b) mandates that the Secretary of the USDA is authorized to cooperate with the officials of the various States or political subdivisions in carrying out the purposes of ensuring animal welfare, which includes any State, local, or municipal legislation or ordinance on the same subject.
Allow multiple survival surgeries to reduce the number of animals used.	Multiple survival surgeries are already allowed under Title 9 Chapter 1 Section 2.31(d)(1)(x)(A). It states an animal is to undergo only one major operative procedure for which it is allowed to recover unless scientifically justified in writing, or as authorized by the attending veterinarian, or as determined as a special circumstance by USDA.
USDA should review regulations and policies of other federal agencies for areas where their requirements are in conflict. Institutions should not be cited by USDA for complying with CDC regulations. (e.g., requirements for the importation of nonhuman primates transported from the port of entry to a CDC-approved quarantine facility.)	Under the AWA Section 2145(a) the Secretary of Agriculture is to consult and cooperate with other federal agencies regarding the welfare of animals. USDA will consider restraints from other federal regulations when evaluating any enforcement situation.
USDA to revise §2.31(c)(3) of the AWR as follows: *The IACUC may, at its discretion, determine the best means of conducting an evaluation of the institution's programs and facilities that includes all members wishing to participate in the process. The IACUC may invite ad hoc consultants to assist in conducting the evaluation. However, the IACUC remains responsible for the evaluation and report.*	Under Title 9 Chapter 1 Section 2.31(c)(3), an IACUC can use subcommittees that consist of a minimum of two IACUC members and may invite ad hoc consultants to assist in conducting evaluations. USDA will not propose a regulatory change; however, USDA will consider providing clarification on how an IACUC may use subcommittees comprising of two members.
USDA to require program reviews annually rather than semiannually. Section 2143(b)(3) of the AWA requires only a semiannual inspection of animal study areas and facilities, but Section 2.31(c)(1-3) of the AWR requires both semiannual inspections and program reviews.	Section 2143(b)(3) of the AWA requires a semiannual inspection of animal study areas and facilities, and section 2.31(c)(1-3) of the Animal Welfare Regulations require both semiannual inspections and program reviews. Lengthening the period of time between program reviews conducted by the IACUC from every six months to every 12 months could impact animal welfare and the monitoring of their health and wellbeing.
Amend 7 U.S.C. § 2137 and § 2138 of the AWA to prohibit the use of random source dogs and cats in research.	• Section 753 of the Omnibus Appropriations Bill of 2016 states none of the funds made available by this Act may be used to carry out any activities or incur any expense related to the issuance of licenses under section of the AWA (7 U.S.C. § 2133), or the renewal of such licenses, to class B dealers who sell dogs and cats for use in research,

	experiments, teaching, or testing. This language carried forward to USDA's fiscal year 2017 and 2018 appropriations and remains in effect. • USDA interprets the legislation to prohibit a class B dealer from using his or her licenses to sell live dogs and cats for use in research, experiments, teaching, testing, or surgery.
IACUC decisions should not be second-guessed by AC Inspectors. There is no statutory or regulatory basis for this review. Under the statute, this authority is assigned to the IACUCs. Inspectors do not have the expertise needed to determine if the IACUC made a correct decision.	USDA inspectors do not second guess the IACUC; inspectors apply the AWA and regulatory requirements. If a research facility is unable to resolve its concerns with the inspector during the inspection process, and the issue results in a finding of noncompliance on an inspection report, the research facility can appeal the finding in the inspection report.
Remove DMR because it is in violation of AWA.	• Section 2143 of the AWA gives the Secretary the authority to promulgate standards to govern the humane handling, care, treatment, and transportation of animals by research facilities. The standards for research facilities include requirements for animal care, treatment, and practices in experimental procedures to ensure that animal pain and distress are minimized, including adequate veterinary care with the appropriate use of anesthetic, analgesic, tranquilizing drugs, or euthanasia. The Secretary shall require a research facility to establish at least one committee. A quorum is required for all formal actions of the IACUC. • The Secretary has promulgated the regulation with respect to IACUC review of research activities involving animals. Under Title 9 Chapter 1 Section 2.31(d)(2), prior to IACUC review, each member of the Committee shall be provided with a list of proposed activities to be reviewed. Written descriptions of all proposed activities that involve the care and use of animals shall be available to all IACUC members, and any member of the IACUC may obtain, upon request, full Committee review of those activities. If full Committee review is not requested, at least one member of the IACUC, designated by the chairman and qualified to conduct the review, shall review those activities, and shall have the authority to approve, require

	modifications in (to secure approval), or request full Committee review of any of those activities.
NIH-specific Topics	**Working Group Analysis and Proposed Actions**
Determine length of protocol review by duration of funding mechanism (e.g., R01 for five years, R03 and R21 for three years)	Extending the period of approval is a risk to animal welfare, as investigators are not able to predict sufficiently to describe their proposed animal experiments in the detail required for adequate IACUC review and approval for the entire five years of a grant. Protocols are frequently amended during the three-year approval period to accommodate changes in experimental design. Performing work not described in a protocol is the most frequently occurring noncompliance reported to NIH OLAW with the current three-year renewal requirement. Extending the period to five years would exacerbate the risk of noncompliance. In addition, grants have different award periods (not all are five years) and there are no requirements for a one-to-one match of protocol to grant. Matching protocol approval to a grant approval decreases the flexibility that institutions currently have with a single protocol covering multiple grants or vice versa.
Stop requiring grant congruency reviews. Grant progress reports would catch substantive discrepancies between the work funded and the work performed, without adding to burden. Harmonize grant congruency more with financial compliance requirements and less on IACUC review and animal procedures, especially in later years of grant.	PHS Policy and the NIH Grants Policy Statement (NIH GPS, chapter 4.1.1.2) require the institution to verify, before award, that the IACUC has reviewed and approved those components of grant applications and contract proposals related to the care and use of animals. This is not an explicit requirement for the IACUC to do a side-by-side comparison of an application or proposal and the IACUC protocol. However, institutions are responsible for ensuring that the information the IACUC reviews and approves is congruent with what is in the application or proposal. Grant-to-protocol congruency is required by NIH only at the first time of competitive award. Institutions are free to devise a workable mechanism to accomplish this end. One method to prevent inconsistencies between the information submitted to PHS and that on the IACUC protocol is to implement a procedure for direct comparison. Some institutions have delegated this responsibility to a particular office or position (e.g., sponsored programs or compliance office).

Have a study section, not IACUC, approve the justification of animal numbers.	Review of proposed activities by a Scientific Review Group (SRG), also known as a study section, is required by the NIH Grants Policy Statement (Part I., 2.4 The Peer Review Process) and federal law (sections 406 and 492 of the Public Health Service Act, as amended by the NIH Reform Act of 2006). If the proposed research includes the use of animal subjects, review of the VAS and proposed animal experiments is conducted by the SRG. After determination of an award, but before release of funds, IACUC review and approval ensures compliance with the PHS Policy and the institution's Assurance. Compliance with PHS Policy is a term and condition of the NIH Grants Policy Statement (Part II, Subpart A 4.1.1 Animal Welfare Requirements) to obtain PHS funds. In 2016 NIH revised the grant application to remove redundancy with IACUC review while meeting the requirements of the PHS Policy. The changes simplify the VAS criteria and reduce the burden on applicants and reviewers. The justification for the number of animals is no longer required in the VAS and is instead an element of rigor in the experimental design, described in the Research Strategy section of the application, and considered during SRG review. Because the IACUC review does not coincide with an awarded grant application, the review must consider the rationale for the approximate number of animals to be used and that the number proposed is necessary to obtain valid results as required by PHS Policy.
OLAW should not view IACUC-approved alternative strategies from "should" statements in the NAS *Guide* as departures or deviations. OLAW should not use the NAS *Guide* as a regulatory document.	NIH OLAW does not support this approach, as such a change would negatively impact animal welfare. Since the adoption of the PHS Policy in 1985, the NIH has required that Assured institutions base their programs of animal care and use on the NAS *Guide*, a respected resource of best practices in the humane care and use of laboratory animals prepared by leading international subject matter experts. The PHS Policy IV.B.3. requires that: "The IACUC shall prepare reports of their semiannual program reviews and animal facility inspections and submit the reports to the Institutional Official (IO). The reports must contain a description of the nature and extent of the institution's adherence to the *Guide* and the PHS Policy, must identify specifically any departures from the provisions of the *Guide* and the PHS Policy, and must state the reasons for each departure." "Should" statements in the NAS *Guide* are standards in animal care and use practiced universally by the biomedical research community to ensure animal welfare. Deviation from a "should"

	statement that is not described as an exception in the NAS *Guide* or as a result of a performance standard must be reported to the IO. Risk aversion practices on part of institutions contribute to any burden from this requirement of the PHS Policy. There is flexibility with the use of performance standards and OLAW's current guidance offers flexibility for professional judgment at the institution for "should" statements in the NAS *Guide*.
Harmonize OLAW's requirement of noncompliance reporting to require the same reporting as USDA.	• The PHS Policy, section IV.F.3., requires that: "The IACUC, through the Institutional Official, shall promptly provide OLAW with a full explanation of the circumstances and actions taken with respect to: 1) any serious or continuing noncompliance with this Policy; 2) any serious deviation from the provisions of the *Guide*; or 3) any suspension of an activity by the IACUC." All institutions with Animal Welfare Assurances (Assurance) are required to comply with the PHS Policy. OLAW plans to review the guidance in NIH Guide Notice NOT-OD-05-034 on reporting requirements to refine and update examples of reportable situations, examples of situations not normally reported, the timeframe for reporting, and the information to be reported. • Under Title 9 CFR Section 2.31(d)(7), the only noncompliance reporting requirement is if the IACUC suspends an activity involving animals, the Institutional Official, in consultation with the IACUC, shall review the reasons for suspension, take appropriate corrective action, and report that action with a full explanation to APHIS and any federal agency funding that activity. • In addition, USDA has instituted a voluntary process to incentivize registrants to self-identify, self-correct, and voluntarily-report serious noncompliance. This will affect how and when facilities are cited for serious noncompliance. The incentives encourage facilities to proactively self-identify areas of noncompliance and take swift action. Non-critical noncompliance will not be cited on inspection reports if the facility discovers the noncompliance on its own and immediately take appropriate correct action to establish measure to prevent reoccurrence. Critical noncompliance will not be cited on the report if the facility discovered the noncompliance on its own, in a

	timely manner, took immediate and appropriate corrective action and establishes measures to prevent recurrence, had no repeat or critical noncompliance at that site in the last 12 months, and has not had a critical noncompliance in the same section and subsection of the regulations within the last 24 months at the same site.
Do not require a grant number on a noncompliance report.	Since provision of the grant number in a report of noncompliance is a requirement of NIH Guide Notice NOT-OD-05-034, this requirement will be reevaluated during review of this notice.
OLAW website suggestions: • Have examples of lay language for different kinds of studies. Many PIs have no idea how to write this part, especially if they are not native English speakers. • Statistics: Have a page on the OLAW website that explains how to do statistics properly and has a user-friendly calculator (similar to the one at http://hedwig.mgh.harvard.edu/sample_size/size.html) • Literature search: Some PIs just plug a bunch of unrelated search terms into PubMed, get no results, and think they are done. A section on the OLAW website on how to do proper literature searches (with examples) would help.	• NIH OLAW plans to consider these suggestions for website aids in coordination with USDA. • Under AWA Section 2143(d) the research facility is to provide training to scientists in experimentation and testing methods that eliminate the use of animals or limit pain and distress. AWA Section 2143(e) establishes the National Library of Medicine (NLM) and the National Agricultural Library (NAL) to provide information on improved methods that reduce or replace animal use or minimize pain and distress. Title 9 Chapter 1 Section 2.32(d)(5) requires training in the utilization of the services of the NLM and NAL. In addition, to assist the regulated community in this effort, the USDA through the Animal Welfare Information Center will continue to: (1) be a resource to identify alternatives to the use of live animals in research (9 CFR Section 2.32(c)(5)) or alternatives to procedures that may cause more than momentary or slight pain or distress to the animals in accordance with 9 CFR Section 2.31(d)(1); (2) provide instruction on identifying alternatives; and (3) provide information on methods that reduce or replace animal use in research or refine techniques to minimize pain and distress on its website. https://www.nal.usda.gov/awic.
FDA-specific Topics	**Working Group Analysis and Proposed Actions**
The RFI does not address the issue of FDA's proposed Good Laboratory Practice (GLP) regulations because of the ongoing regulatory process surrounding Docket No. FDA-2010-N-0548 GLP for Nonclinical Laboratory Studies. As such, previous comments made in response to that docket are reiterated: The proposed rules are redundant, confusing,	As noted by the commenters, FDA's rulemaking with respect to part 58, GLP for Nonclinical Laboratory Studies (GLP rulemaking) (Docket No. FDA-2010-N-0542) is still ongoing. Any comments made in response to

and inconsistent with existing language in the AWA or PHS Policy. Rather than create new requirements, FDA should continue to work closely with USDA and NIH under the existing MOU agreement and focus on assuring that proper documentation is in place to allow the federal regulatory agency responsible for the applicable statute or standard to determine compliance.	the RFI regarding the subject of the GLP rulemaking may be taken under advisement as finalization of the proposed rule is considered.
Many FDA regulations currently require that drug sponsors submit data derived from animals, hampering companies' ability to use and submit non-animal methods. Yet those non-animal methods, including organs-on-a-chip, are becoming increasingly available and robust. FDA should remove its requirements for animal data to reduce burden and ensure the longevity of the regulations in the face of rapidly advancing human-based science.	The FDA is continually working to reaffirm and strengthen its commitment to replacing, reducing, and refining animal studies and supports the development and use of alternative methods (such as assays and technologies like organs-on-a-chip). As part of that commitment, the FDA had previously formed the Modeling and Simulation Working Group to accelerate the adoption of modeling and simulation tools in product development and evaluation; and initiated the Toxicology Working Group, which has developed a Roadmap for integrating emerging predictive toxicology methods and new technologies into regulatory safety and risk assessments. The FDA also participates in and chairs the Interagency Coordinating Committee on the Validation of Alternative Methods. The agency is optimistic that cultivating these types of new technologies can continue to reduce the need for animal testing. However, it is important to recognize that there are still many areas where animal research is important and necessary to evaluate the safety and efficacy of potential products under FDA's regulatory jurisdiction, for example, when non-animal testing for a particular endpoint is not yet a scientifically valid or available option. .
Animal-related Topics	**Working Group Analysis and Proposed Actions**
Apply PHS Policy to all animals used for experiments.	This suggested approach is outside the scope of the Working Group and would require statutory changes.
Extend AWA protection to birds, rats, mice, horses, other farm animals, and all animals.	This suggested approach is outside the scope of the Working Group and would require statutory changes.
NIH, FDA, and USDA should encourage use of non-animal methods and development of alternatives.	• PHS Policy, the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, the NAS *Guide,* and the VAS of the NIH grant application direct IACUCs and investigators to consider reduction, refinement, and replacement and apply where appropriate. For example, the Policy,

in Section IV.C.1., expects IACUCs to confirm that research with animals is consistent with the NAS *Guide* and the *Guide*'s endorsement of the 3Rs; US Government Principle III is about reduction and replacement of animals; US Government Principle IV describes refinements to minimize pain and distress; the VAS requires the use of alternatives unless the research goals cannot be accomplished using an alternative model.

- Under AWA Section 2143(d) the research facility is to provide training to scientists in experimentation and testing methods that eliminate the use of animals or limit pain and distress. AWA Section 2143(e) establishes an information service at the National Agricultural Library (NAL). The services, in cooperation with the National Library of Medicine (NLM), provide information on improved methods that reduce or replace animal use or minimize pain and distress. Under Title 9 Chapter 1 Section 2.32(d)(5), training must include guidance in the utilization of the services (e.g., NLM and NAL) available to provide information on: appropriate methods of animal care and use, alternatives to the use of live animals in research, that which can prevent unintended and unnecessary duplication of research involving animals, and the intent and requirements of the AWA. In addition, to assist the regulated community in this effort, USDA through the Animal Welfare Information Center will continue to: (1) be a resource to identify alternatives to the use of live animals in research (9 CFR Section 2.32(c)(5)) or alternatives to procedures that may cause more than momentary or slight pain or distress to the animals in accordance with 9 CFR Section 2.31(d)(1); (2) provide instruction on identifying alternatives; and (3) provide information on methods that reduce or replace animal use in research or refine techniques to minimize pain/distress on its website https://www.nal.usda.gov/awic.
- FDA is committed to animal welfare and supports the development and use of alternative methods (such as assays and technologies like organs-on-a-chip) that reduce, replace, and refine animal use in research. Therefore, the use of nonclinical models as alternatives to animal use is not discouraged when they are predictive of processes

	verifying the assessment of safety and efficacy in humans. Although these alternative methods to animal use are highly encouraged, there are instances when they do not provide scientifically valid data predictive of safety and efficacy. Also, these methods proposed may not have been validated to predict safety risks. When the safety and efficacy of potential products under FDA's regulatory jurisdiction are questionable due to limitations with alternative methods, or there are no alternative methods for safety and efficacy studies, animal research is necessary. For this reason, limitations of alternative methods for assessing safety and efficacy must be taken into consideration to maintain the health and safety of the public.
Database-related Topics	**Working Group Analysis and Proposed Actions**
• Create a national database of standard acceptable practices with broad ranges of variances (for instance, range of doses, types of adjuvants [immunization/vaccination models]), and a broad definition of *de minimus* that will not and should not concern OLAW. Mandate that IACUCs accept a simple mention of a procedure that is within the parameters identified in the database. • Use an algorithmic-based, computerized system. Generate animal protocols for the most commonly encountered procedures (e.g., transgenic breeding, blood sampling, euthanasia, tissue sampling), as well as more specialized procedures. Require more advanced training to ensure that those who use the database understand the principles of animal treatment, breeding, and handling.	NIH does not mandate procedures but rather supports the use of evidence-based performance standards to foster good science while ensuring animal welfare. • NIH OLAW, in coordination with USDA, will continue to support the efforts of FDP members to create the CUSP repository. After the CUSP repository is piloted by FDP institutions, NIH OLAW, in coordination with USDA, plan to offer resources to IACUCs to integrate CUSP into their institutional processes to reduce burden on investigators. Use of the CUSP would be optional and open-access. • NIH OLAW, in coordination with USDA, will continue to support the efforts of the IAA to create a repository of IACUC best practices. After the repository is piloted by IAA, NIH OLAW, in coordination with USDA, plan to offer resources to IACUCs to integrate the best practices into their institutional processes to reduce burden on investigators. Use of the IAA repository would be optional and open-access.
IACUC-related Topics	**Working Group Analysis and Proposed Actions**
Changes which may not affect animal health (drug dose, change in sampling time) should be considered minor changes and should not require IACUC review.	• NIH, in coordination with USDA, plan to review and enhance resources to support IACUC use of existing options that streamline protocol review and significant changes to approved protocols.

	• Title 9 CFR § 2.31(d)(1-5) regulations do not address minor changes to the research activities. It is therefore up to the IACUC to determine how to address minor changes.
Scientific review should be conducted by a study section, not IACUC.	Peer review of the scientific and technical merit of an application is the purview of the NIH Scientific Review Groups (SRGs). SRGs have authority to raise specific animal welfare concerns that require resolution prior to grant award. Although not intended to conduct peer review of research proposals, the IACUC is expected to include consideration of the US Government Principles in its review of protocols. US Government Principle II calls for consideration of the relevance of a procedure to human or animal health, the advancement of knowledge, or the good of society. Other PHS Policy review criteria refer to sound research design, rationale for involving animals, and scientifically valuable research. A study that could not meet these basic criteria is inherently unnecessary and wasteful and, therefore, not justifiable. The primary focus of the SRG is scientific merit, and the primary focus of the IACUC is animal welfare. The two bodies have differing constitutions, mandates, and functions. However, it is not possible to separate scientific value from animal welfare. Some overlap is inevitable and fosters accountability in the oversight system. SRGs may raise concerns about animal welfare and IACUCs may question the scientific rationale or necessity for a procedure.
Mandate a uniform animal protocol form so investigators moving between institutions do not waste time converting between institution-specific forms.	NIH OLAW supports a flexible approach to foster good science while ensuring animal welfare. NIH OLAW will consider updates to simplify its sample animal study protocol form and pilot the revised protocol form through FDP.
Occupational Health and Safety Program (OHSP) Topics	**Working Group Analysis and Proposed Actions**
There is no statutory authority for the requirements in the PHS Policy for a health and occupational risk program. Of course, institutions have such programs and may choose to implement them through the IACUC. An IACUC should not reject a protocol on the basis of occupational safety and health concerns. By doing so, it is using the AWA and/or Health Research Extension Act to enforce requirements that are not provided for in those statutory authorities.	NIH OLAW does not support this approach. Based on the Public Health Service Act, NIH OLAW has statutory authority to require an occupational health and safety program. The PHS Policy (Section IV.A.1.f.) requires a "health program for personnel who work in laboratory animal facilities or have frequent contact with animals." The NAS *Guide* states that, "Each institution must establish and maintain an occupational health and safety program as an essential part of the overall Program of animal care

	and use… The nature of the OHSP will depend on the facility, research activities, hazards, and animal species involved." (*Guide* pages 17-23) "A comprehensive OHSP should include a hierarchy of control and prevention strategies that begins with the identification of hazards and the assessment of risk associated with those hazards." (*Guide* page 18) An effective occupational health and safety program must encompass all personnel who have contact with animals. Depending on the species of animal or the amount of animal exposure, the program may not affect all personnel equally. Minimally, the program must include: 1) pre-placement medical evaluation; 2) identification of hazards to personnel and safeguards appropriate to the risks associated with the hazards; 3) appropriate testing and vaccinations; 4) training of personnel regarding their duties, any hazards, and necessary safeguards; 5) policies and facilities that promote cleanliness; 6) provisions for treating and documenting job-related injuries and illnesses; 7) facilities, equipment, and procedures designed, selected, and developed to reduce the possibility of physical injury or health risk to personnel; 8) good personal hygiene practices, prohibiting eating and drinking, use of tobacco products, and application of cosmetics and/or contact lenses in animal rooms and laboratories; and 8) personal protective equipment.
Oversight Topics	**Working Group Analysis and Proposed Actions**
• Have one agency that covers all species regardless of funding source. It should be USDA because they have legal authority to enforce regulations. • Harmonize all standards of both agencies to highest standard and cover all vertebrate species. • Duplicate research is necessary for rigor and reproducibility.	The US government is organized with various agencies responsible for oversight of different functions. These agencies operate under various mandates, regulations, and guidelines, with overlapping areas of authority. NIH OLAW, USDA, and FDA cooperate to harmonize oversight of research animal subjects as described earlier in this report. NIH OLAW operates by authority of the Public Health Service (PHS) Act; USDA operates under the authority of the AWA and Animal Welfare Regulations; and FDA operates under the authority of the Federal Food, Drug, and Cosmetic Act and the PHS Act.
IACUC Inspections Topics	**Working Group Analysis and Proposed Actions**
• Allow IACUC inspections to occur once per year instead of twice.	NIH OLAW and USDA do not support this approach, as it would negatively impact animal welfare. As described in the NAS *Guide*, the responsibility of the IACUC is to oversee and routinely evaluate the

• Reduce semiannual inspection duration for investigators who maintain good inspection records with IACUC. Maintain semiannual inspections for those who do not.		program of animal care and use (*Guide* page 24). Both the Health Research Extension Act and the AWA require the IACUC to inspect animal care and use facilities, including sites used for animal surgeries, every six months. A change in the frequency of IACUC inspections would require statutory changes to both laws. The PHS Policy allows flexibility in how and by whom the inspections are conducted. NIH OLAW in coordination with USDA plan to develop guidance to address existing flexibilities. A statutory change to AWA 2143(b)(3) regarding IACUC semiannual inspections requires approval from Congress. The implementing regulations under Title 9 CFR Section 2.31(c)(3) provide flexibility in allowing the IACUC to determine the best means to conduct program and facility evaluations.

B1: Encourage the use of sections of the AAALAC International program description in applicable parts of the OLAW Animal Welfare Assurance for institutions accredited by AAALAC International		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments on why agencies should adopt B1. • it would enable a more efficient path to consistency between the two documents • it would save months of writing, rewriting, and reviewing proposals because of the descriptive language used • institutions already do this • it is okay to do this, but it will not reduce burden on investigators	Public comments on why agencies should not adopt B1. Would not solve the problem: • this would not apply to all Assured institutions • OLAW shouldn't be using international guidelines • not many applicable sections Not in the interest of animal welfare: • institutions should be encouraged to give more thought to the nature of their programs. Allowing them to copy and paste doesn't encourage thoughtful reflection on whether appropriate standards and programs are being implemented to	NIH OLAW plans to change the instructions to the domestic Animal Welfare Assurance to support the use of certain elements of the AAALAC program description to enable consistency and limit rewriting of responses relevant in both documents.

	minimize the pain, discomfort, and distress endured by animals	
Public comments on how agencies should adopt B1. • Harmonize the wording of the common sections • develop abbreviated Assurance for AAALAC accredited programs to address areas specific to PHS Policy that are not included in the AAALAC program description • use the same questions in the OLAW Assurance that are in the AAALAC program description • allow AAALAC accreditation in lieu of OLAW Assurance to reduce burden, provide a single-source document, and streamline efforts • allow institutions to use Assurance as part of their AAALAC program description so that AAALAC could take advantage of what many of their member facilities are already creating and providing to OLAW • ensure that no information currently provided to OLAW is left off due to this change • use best practices from both programs		NIH OLAW plans to coordinate with AAALAC about options for harmonizing documents to meet both organizations requirements.
Make domestic Assurance simpler by: • overhauling domestic Assurance from prescriptive document to a simple acknowledgment that the institution is adhering to the spirit of NIH regulations • abbreviating the Assurance document, which could be as simple as a statement from the IO describing the applicability of		The PHS Policy section IV.A. defines the specific elements required in the domestic Animal Welfare Assurance, which include: 1) a description of the institution's program of animal care and use; 2) demonstration of institutional commitment to the humane care and use of animals; and 3) how compliance oversight will be provided. Changes to the

the Assurance in terms of the overall animal care program. This would be followed with a list of questions specific to the various subsections of IV.A. of the PHS Policy. These questions would affirm that the specific subsection is addressed in the institutional description or, if not, would require a description of the institution's method for meeting the requirements of the specific subsection.	required elements in the PHS Policy are not anticipated.
Adopt Office for Human Research Protections-style Assurance. The Office for Human Research Protections has reduced the length of its Federalwide Assurance document without endangering human research subjects. NIH OLAW may be able to do the same for animal research.	The condition of human subjects used in research differs from the condition of animals and therefore requires different oversight and regulation. The PHS Policy is explicit about the required elements in the Animal Welfare Assurance to provide oversight of animal welfare for PHS-funded activities.
Why do AAALAC International accredited programs in foreign countries have a three-page Assurance, while accredited programs in the US are referred to a 13-page domestic Assurance sample document?	The PHS Policy is explicit about the required elements in the domestic Animal Welfare Assurance. PHS Policy section II allows institutions in foreign countries receiving PHS support for activities involving animals to either comply with the Policy or provide evidence to the NIH OLAW that acceptable standards for the humane care and use of the animals in PHS-conducted or supported activities will be met.
Regarding the Freedom of Information Act: • AAALAC may be required to obey the Freedom of Information Act if it interacts with OLAW • if OLAW obtains information about a research facility from AAALAC, then AAALAC information should be and is subject to public inspection	NIH OLAW does not and will not obtain institutional information from AAALAC for the Animal Welfare Assurance document. The Freedom of Information Act only applies to documents in a federal agency's possession at the time of a request.

B2: Encourage the use of the FDP Compliance Unit Standard Procedures as a repository of best practices for standard procedures used for research with animals		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**

Public comments on why agencies should support B2.
• it would be a valuable resource for investigators, reduce administrative burden, and improve consistency in research with animals
Public comments on how agencies should support B2.
• it needs to be open access, freely available to the public and all research institutions in the US
• allow animal welfare experts and veterinarians to contribute best practice suggestions
• public comments should be encouraged and accepted
• there should be a way to explore further improvement and implementation of even better practices
• OLAW should clearly state that any best practices or standard procedures do not carry any legal or regulatory force
• committee and institutional diversity may result in resistance to accept procedures as a best practice. It may be feasible to develop procedures based on evidence (e.g., blood collection, euthanasia) that are commonly used by all institutions
• it has to be evidence-based and its content systematically reviewed; any deviations
	Public comments on why agencies should not support B2.
	• it would not reduce the burden due to the individualistic nature of all our research institutions; what is acceptable to one may not be acceptable to another, and they might have valid reasons for this
	• do not support encouraging institutions to use the FDP CUSP; there is inadequate information to assess if the resource will reduce the burden
	• the burden associated with contributing to, reviewing, managing, and using the CUSP database is unknown and not well-described
	• because CUSP is in pilot testing, a decision should be made after testing is complete and impact is reviewed
	• require mandatory use of CUSP as a repository of best practices for standard procedures
	  ○ institutions involved in animal research should have to apply for licenses annually
	  ○ institutions should have mandatory training and federal protocols in place to ensure the safety of the animals and assure the public
		NIH OLAW in coordination with USDA will continue to support the efforts of FDP members to create the CUSP repository. After the CUSP repository is piloted by FDP institutions, NIH OLAW in coordination with USDA plan to offer resources to IACUCs to integrate CUSP into their institutional processes to reduce burden on investigators. Use of the CUSP repository would be optional and open-access.

from the descriptions in the repository need to be justified and described in detail by the investigator • the platform should be regularly maintained and operated by dedicated, knowledgeable personnel who are available to assist users in an efficient manner		
B3: Encourage the use of the IACUC Administrators Association repository of Best Practices by IACUCs		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments on why agencies should support B3. • to encourage consistency and regulatory compliance • access to best practices proposed by a wide array of IACUC administrative professionals provides an excellent source of information about trends in the field, novel situations, implementation challenges, or solutions • since all are trying to follow the same guidelines, it makes sense to try to standardize their approaches and policies Public comments on how agencies should support B3. • provide guidance / standard operating procedures to researchers • standardize as much as possible • it must be open-access if endorsed by OLAW • OLAW must clearly state that use is not mandatory and documents do not have legal or regulatory authority	Public comments on why agencies should not support B3. • they may come up with more rules and regulations rather than reducing them • a repository is dependent on what is voluntarily posted, is not readily accessible to all, and has limited information available • it should not be a member only resource, which blocks transparency and limits public participation. • best practices cannot replace clear guidance from regulatory agencies and should not be construed as mandates	NIH OLAW, in coordination with USDA, will continue to support the efforts of the IAA to create a repository of IACUC best practices. After the repository is piloted by IAA, NIH OLAW, in coordination with USDA, plan to offer resources to IACUCs to integrate the best practices into their institutional processes to reduce burden on investigators. Use of the IAA repository would be optional and open-access.

- It should be kept up-to-date and be evidence-based and unbiased
- formal NIH support for this resource could increase its use and maintenance
- a standard operating procedure repository is useful, but do not call it best practices, as this will lead to additional self-imposed regulatory burden

B4: Encourage the use of new or existing tools to streamline protocol review through use of Designated Member Review (DMR), DMR subsequent to full committee review, and/or Veterinary Verification and Consultation		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments about why agencies should support B4. • use of VVC should reduce unnecessary burden and also benefit animal welfare • it would streamline review • because they are faster, they could be implemented at any time • the method has already been implemented by many institutions • it is already encouraged by OLAW and USDA, and has reduced burden for institutions that choose to utilize it • VVC shows that PHS Policy can be used to facilitate processes without negatively impacting animal welfare Public comments on how agencies should support B4. • explain specific circumstances where each option would be applied • adopt risk-based assessment of protocol procedures and permit an administrative or	Public comments about why agencies should not support B4. • existing tools do not reduce the burden on investigators • it makes review more burdensome for IACUC administrators • protocols that go to FCR often have more thorough reviews; when AAALAC finds one of our protocols has problems, it is usually a protocol that went through DMR • it may help in theory, but VVC is made excessively complex by institutions adding additional burden on the process	• NIH OLAW, in coordination with USDA, plan to review and develop enhanced resources to support IACUC use of existing options that streamline protocol review and significant changes to approved protocols without compromise to animal welfare. • The Secretary has promulgated the regulation with respect to IACUC review of research activities involving animals. Under Title 9 Chapter 1 Section 2.31(d)(2), prior to IACUC review, each member of the Committee shall be provided with a list of proposed activities to be reviewed. Written descriptions of all proposed activities that involve the care and use of animals shall be available to all IACUC members, and any member of the IACUC may obtain, upon request, full Committee review of those activities. If full Committee review is not requested, at least one member of the IACUC, designated by the chairman and qualified to conduct the review, shall review those activities, and shall have the

VVC-like review process for new submissions utilizing only low-risk procedures (e.g., blood draw, euthanasia without manipulation for tissue collection, breeding colonies)

- expand VVC (e.g., rather than limit the veterinarian to confirming compliance with an IACUC policy, give the veterinarian the authority to approve modifications that the veterinarian has the authority to oversee such as treatments, anesthetics, analgesics, and euthanasia; this could be expanded, with the authority of the IACUC, to other procedures as well)
- support the creation of clear definitions and decision tools to aid risk-based reviews
- OLAW should simplify the VVC process and trust the professional judgement of veterinarians to determine what significant changes can be approved
- some IACUCs are hesitant to use VVC due to confusion over how it should be implemented
- the research community, IACUC members, vets, and PIs would be well-served if OLAW were more forthright about what is and is not required to use the VVC process. (e.g., institutions are not required to develop an IACUC-approved formulary of drugs for reference by the veterinarians during VVC of changes in anesthesia, analgesia, or sedation; or policies on duration of each procedure used at that institution; exactly how many extra blood draws can be approved; frequency of each procedure used at that institution; nor on a specific authority to approve, require modifications in (to secure approval), or request full Committee review of any of those activities.

number allowable when considering an increase in previously approved animal numbers)

B5: Expanded IACUC training activities that focus on reducing burden on investigators		
Agree	**Disagree**	**Working Group Analysis and Proposed Actions**
Public comments about why agencies should support B5. • support expanded IACUC trainings that focus on reducing investigator burden • training to reduce burden may help an institution implement practices that could reduce burden on investigators • expanding IACUC training that focuses on reducing the burden on investigators and on IACUC administrative offices would be helpful Public comments about how agencies should support B5. • place appropriate focus on animal welfare while removing undue administrative burden, clarifying recommendations versus requirements, and offer resources to investigators • offer such training to a randomly selected group of IACUCs and compare their post-training implementation of PHS Policy and AC regulations to that of untrained IACUCs; if it is more efficient and less burdensome, then offer it to all; offer such training to the IO and compliance officers because the cautious approach emanates from those officials and not the IACUC	Public comments about why agencies should not support B5. • expanded IACUC training may increase burdens if the institution makes it mandatory • existing training requirements are already too burdensome • there is more than enough training via OLAW, USDA, American Association for Laboratory Animal Sciences, published literature, and regional conferences • it does not reduce the burden, because training is implemented on an institutional level; instead, USDA & OLAW should identify what is and is not legally required Public comments about how agencies should not support B5 but instead should: • provide training activities that include meaningful, comprehensive instruction • provide training that focuses on the 3Rs, not the reduction of burden • provide more training of how to meet IACUC mandate, not on instructing members to reduce burden • expand IACUC training that focuses on areas where IACUC failures have been documented	NIH OLAW, in coordination with USDA, will continue to support the development of industry-led training and resources to assist institutional leadership, IACUC members, and IACUC administrators in reducing the administrative burden on investigators.

- alternatives to expensive in-person training sessions would be helpful given budgetary constraints
- it could be useful if included in a repository of other training materials for IACUC members
- support training that reinforces evidence-based interpretation and implementation of regulations and policies
- support training that uses best practices for pedagogy and includes formal assessment of mastery of concepts, facts, and learning objectives
- develop a checklist of best practices that IACUCs could use as a self-assessment tool to identify opportunities to remove burden from administrative offices
- support grants to the community for developing and sharing materials that promote efficient practices
- consider highlighting existing efforts to reduce burden as a means of raising awareness
- provide more resources on effectively and efficiently training researchers about the regulations and practical aspects of their work
- highlight the non-binding nature of guidance and the flexibility provided in regulation and policy

B6: Other tools or resources not previously mentioned*

***Because of the open-ended nature of this topic, the RFI responses have been grouped by broad topic areas or agency-specific topics where applicable**

General Multi-agency Topics	Working Group Analysis and Proposed Actions
Encourage a similar dialog with the Department of Defense and the Department of Veterans Affairs concerning the use of animals in	Although outside the scope of the 21CCA 2034(d), NIH OLAW, in coordination with USDA, plan to engage with the Department of Defense

research. Separate requirements increase the burden on investigators who receive funding from these sources.	and the Department of Veterans Affairs about options for harmonizing requirements to reduce administrative burden on investigators who receive support from multiple federal agencies to conduct research with animals.
Clarify the distinction between regulation and policy. The regulatory tone in agency guidance and expectations that institutions follow guidance, as in the case of OLAW's FAQs and Notices and the USDA's Animal Care policies, can disproportionately influence decision-making by institutions seeking to mitigate compliance risks. Although the description of these guidance documents often includes terms like *advice, guidance, best practices*, and *recommendations*, the true meaning behind these terms is not conveyed in oversight and enforcement. Agencies should include a general statement underscoring the fact that their policies and guidelines do not establish legally enforceable responsibilities. Agencies should clarify that *guidance* describes the agency's current thinking on a topic and should be viewed only as recommendations of how institutions could meet the statutory requirements, with institutions retaining the flexibility to devise other ways to comply with the written regulations.	• NIH OLAW plans to review its disclaimer concerning current guidance to emphasize that "unless specific statutory or regulatory requirements are cited, the guidance should be viewed as recommendations in that an institution may use an alternative approach if the approach satisfies the requirements of the PHS Policy." • The Animal Care policy manual was established in 1997 and revised in 2011. The purpose of the manual was to provide guidance to USDA Animal Care field inspectors and members of the AWA regulated community on how certain provisions of the Animal Welfare regulations should be interpreted. The policy manual was removed from the USDA website in July 2018, and the policies are inoperative, while USDA conducts a review to ensure conformity with the AWA and Animal Welfare Regulations, harmonize with NIH OLAW guidance, and reduce investigator burden where possible. USDA will make any revised and future policies involving the use of animals in research, teaching, testing, experiments, or surgery available for public comment using regulations.gov or a similar service.
Instead of challenging investigators throughout their careers with this yearly paperwork, create a probationary period for training in effective and safe animal use methods for new PIs, wherein protocols are carefully assessed, and then remove the requirement thereafter for submitting any protocols, or only require a new protocol if a new procedure will be used.	• According to Title 9 Chapter 1 Section 2.31(d), in order for the IACUC to approve proposed activities or proposed significant changes to ongoing activities, the IACUC shall conduct a review of those components of the activities related to the care and use of animals and determine that the proposed activities are in accordance with this subchapter unless acceptable justification for a departure is present in writing. Also, 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. • USDA will propose, through notice and comment rulemaking, a regulatory change to Title 9 Chapter 1, Subchapter A-Animal

	Welfare, Section 2.31(d)(5), to remove the requirement that IACUCs conduct "continuing reviews of activities covered by [the Animal Welfare Act] at appropriate intervals . . . but not less than annually," and, instead, insert a requirement that IACUCs conduct a three-year *de novo* review of activities. IACUCs would continue to review, approve, require modification to, or withhold approval of significant changes regarding the care and use of animals in ongoing activities, as required by 9 CFR §§ 2.31(d)(7), 2.31(e). The regulatory change brings alignment between USDA and NIH requirements and reduces the time and effort dedicated to reviewing protocols on an annual basis, while retaining the benefits of a thorough *de novo* review every three years and ongoing review of any significant changes. The IACUC may choose to review a protocol at an interval more frequently than three years as part of conducting a program review. In addition, under AWA Section 2143(d) the facility is to provide training to scientists which include humane practice of animal maintenance and experimentation; and under Title 9 Chapter 1 Section 2.32 the facility is ensure scientists are qualified to perform their duties. This responsibility shall be fulfilled in part through the provision of training and instruction.
USDA-specific Topics	**Working Group Analysis and Proposed Actions**
Decrease the frequency of USDA inspections based on: • risk-based assessments and previous assessments; • consideration of AAALAC full accreditation (e.g., every three years vs annual); or • institutions with no citations or inspection findings.	Section 2146(a) of the AWA states that the Secretary shall inspect each research facility at least once each year, and in the case of deficiencies or deviations from the standards, shall conduct such follow up as deemed necessary. In addition, USDA uses a risk-based inspection system to determine the frequency of inspections based on history of findings. Facilities with inspection histories of no noncompliance are visited annually, while other facilities may be inspected more frequently, depending on the finding, with some undergoing a focused inspection to follow-up on areas of prior noncompliance. Regarding AAALAC, USDA already allows a site visit conducted by AAALAC to substitute for an IACUC semiannual inspection as long as the requirements as set forth in Title 9 Chapter 1 Section 2.31(c) are met.

Incentives for Identifying, Reporting, Correcting, and Preventing Noncompliance with the Animal Welfare Act, creates new policy for the documentation of AWA violations. It states that if a regulated facility violates the AWA, the violation (noncompliance) may be omitted from the facility's inspection report if a few requirements are met. This has made it unclear how research facilities should understand compliance and how facilities might ensure compliance with the AWA.	Animal Care has instituted a voluntary process to incentivize registrants to self-identify, self-correct, and voluntarily report serious noncompliance. This will affect how and when facilities are cited for serious noncompliance. The incentives encourage facilities to proactively self-identify areas of noncompliance and take swift action. Non-critical noncompliance will not be cited on inspection reports if the facility discovers the noncompliance on its own and immediately take appropriate correct action to establish measure to prevent reoccurrence. Critical noncompliance will not be cited on the report if the facility discovered the noncompliance on its own, in a timely manner, took immediate and appropriate corrective action and establishes measures to prevent recurrence, had no repeat or critical noncompliance at that site in the last 12 months, and has not had a critical noncompliance in the same section and subsection of the regulations within the last 24 months at the same site.

Appendix 3. Acronyms Used in the Report

21CCA	21st Century Cures Act, Public Law 114-255
3Rs	Three Rs – Replacement, Reduction, Refinement
AAALAC	AAALAC International
AAMC	Association of American Medical Colleges
AC	Animal Care
APHIS	Animal and Plant Health Inspection Service
AWA	Animal Welfare Act
BP	Best Practices
COGR	Council on Government Relations
CUSP	Compliance Unit Standard Procedures
DMR	Designated Member Review
FAQ	Frequently Asked Question
FASEB	Federation of American Societies for Experimental Biology
FCR	Full Committee Review
FDA	Food and Drug Administration
FDP	Federal Demonstration Partnership
FOIA	Freedom of Information Act
GLP	Good Laboratory Practice
IAA	IACUC Administrators Association
IACUC	Institutional Animal Care and Use Committee
IO	Institutional Official
IRB	Institutional Review Board
NABR	National Association for Biomedical Research
NAL	National Agricultural Library
NAS	National Academy of Sciences
NIH	National Institutes of Health
NLM	National Library of Medicine
NSF	National Science Foundation
OHSP	Occupational Health and Safety Program
OLAW	Office of Laboratory Animal Welfare
PD	Program Description
PETA	People for the Ethical Treatment of Animals
PHS	Public Health Service
PI	Principal Investigator
RFI	Request for Information
USDA	US Department of Agriculture
VVC	Veterinary Verification and Consultation