Working Group on the Use of Chimpanzees in NIH-Supported Research A Working Group of the Council of Councils

January 22, 2013

<u>Co-Chairs</u> Daniel H. Geschwind, M.D., Ph.D. K.C. Kent Lloyd, D.V.M., Ph.D.

For Today

Origin of the Report

- The IOM Report
 - Principles
 - Criteria
- Working Group Charge

The Working Group Organization

- Working Group Members
- Activities
- Working Group Subgroups

The Working Group Report

- Organization of the Report
- Recommendations

Next Steps...

Origin of the Report

The IOM Report

- In December 2010, the NIH asked the IOM to review the current use of chimpanzees in NIH-funded biomedical and behavioral research.
- The IOM committee focused its efforts on the nearly 700 chimpanzees owned or supported by the NIH.
- On December 15, 2011, the IOM issued a report, Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity, summarizing the committee's findings.
- In this report, the committee identified three principles to serve as the basis for its criteria for assessing the use of chimpanzees in biomedical and behavioral research.

CHIMPANZEES IN BIOMEDICAL AND BEHAVIORAL RESEARCH

The IOM Report: Principles

- The knowledge gained must be necessary to advance the public's health;
- 2. There must be no other research model by which the knowledge could be obtained, and the research cannot be ethically performed on human subjects; and
- 3. The animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats.

The IOM Report: Criteria

Biomedical Research:

- 1. There is no other suitable model available, such as in vitro, nonhuman in vivo, or other models, for the research in question;
- 2. The research in question cannot be performed ethically on human subjects; and
- 3. Forgoing the use of chimpanzees for the research in question will significantly slow or prevent important advancements to prevent, control, and/or treat life-threatening or debilitating conditions.

Animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats. Biomedical research using stored samples is exempt from these criteria.

The IOM Report: Criteria

Comparative Genomics and Behavioral Research:

- 1. Studies provide otherwise unattainable insight into comparative genomics, normal and abnormal behavior, mental health, emotion, or cognition; and
- 2. All experiments are performed on acquiescent animals, using techniques that are minimally invasive, and in a manner that minimizes pain and distress.

Animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats. Comparative genomics and behavioral research using stored samples are exempt from these criteria.

The IOM Report

- The IOM concluded that "while the chimpanzee has been a valuable animal model in past research, most current use of chimpanzees for biomedical research is unnecessary."
- The committee also stated that the following areas might continue to require the use of chimpanzees:
 - some ongoing research on monoclonal antibody therapies; research on comparative genomics; and noninvasive studies of social and behavioral factors that affect the development, prevention, or treatment of disease.
- The NIH accepted the IOM committee's principles and criteria and, in February 2012, assembled the Working Group on the Use of Chimpanzees in NIH-Supported Research.

The Working Group Charge Includes:

- Developing a plan for implementation of the IOM's guiding principles and criteria;
- Analyzing currently active NIH-supported research using chimpanzees to advise on which studies currently meet the principles and criteria defined by the IOM report and advising on the process for closing studies if any do not comply with the IOM recommendations;
- Advising on the size and placement of active and inactive populations of NIH-owned or -supported chimpanzees that may need to be considered as a result of implementing the IOM recommendations; and
- Developing a review process for considering whether potential future use of the chimpanzee in NIH-supported research is scientifically necessary and consistent with the IOM principles.

The Working Group Organization

Working Group Members

K.C. Kent Lloyd, D.V.M.., Ph.D. Co-Chair; UC Davis (Veterinary Medicine, Comparative Medicine)

Patricia Turner, M.Sc., D.V.M., D.V.Sc. Ontario Vet. College (Veterinary Medicine)



WG Hepatitis/Virology Consultants: Charles Rice, Ph.D. Rockefeller University Stan Lemon, M.D. University of North Carolina

*Daniel Povinelli, Ph.D. (WG member, retired)

Daniel H. Geschwind, M.D., Ph.D. Co-Chair; UCLA (Neuroscience)

> Alan D. Barrett, Ph.D. Univ. of Texas Medical Branch (Emerging Diseases)

Stephen Ross, Ph.D. Lincoln Park Zoo (Captivity, Behavior)





Beatrice Hahn, M.D. Univ. of Pennsylvania (SIV, Research with wild chimpanzees)

11

R. Alta Charo, J.D. Univ. of Wisconsin

at Madison (Ethics, Legal)

Creation of Working Group and Major Working Group Activities



The Subgroups of the Working Group

Subgroup	Members and/or Consultants	Responsibilities
Colony Management Subgroup	Beatrice Hahn, M.D. Daniel Povinelli, Ph.D.* Stephen Ross, Ph.D. Patricia Turner, M.Sc., D.V.M., D.V.Sc. *from Feb – Sept 2012 only	 Evaluate and make recommendations on the size and placement of colonies of chimpanzees Draft recommendations on the IOM's guiding criteria regarding "ethologically appropriate environments" for chimpanzees
Emerging Diseases Subgroup	Alan Barrett, Ph.D. L. Bill Cummins, D.V.M.* Frederick A. Murphy, D.V.M., Ph.D. * Mark Slifka, Ph.D.* Lee Thompson* *external expert	 Determine whether the use of chimpanzees is necessary to study emerging diseases or develop medical countermeasures Identify the circumstances under which chimpanzees should be used for emerging disease research
Process Review Subgroup	Dan Povinelli, Ph.D.* R. Alta Charo, J.D. Daniel H. Geschwind, M.D., Ph.D. *from Feb – Sept 2012 only	 Evaluate whether one set of metrics/standards could be developed for both biomedical and behavioral/cognitive studies involving chimpanzees Assess and make recommendations regarding the process for determining the future need to use chimpanzees in research
Project Review Subgroup	All Working Group members	 Review active NIH research involving chimpanzees Advise on the process for closing studies that do not comply with IOM recommendations

Information Gathering

- Two (2) Requests for Information (RFI)
- Regular working group meetings (16)
- Subgroup meetings (2)
- Seven (7) field trips to facilities that house and care for chimpanzees, including:
 - Four (4) research facilities
 - The research reserve facility
 - A zoo
 - Two (2) sanctuaries
- Expert interviews (11) to advise on key concepts, such as ethologically appropriate physical and social environments and population size
- Consultants as needed (10)

Experts Interviewed

Name	Title	Expertise
Linda Brent, Ph.D.	President and Director, Chimp Haven, Inc.	Behavioral Primatology
Kathleen Conlee	Vice President, The Humane Society of the U.S.	Animal Welfare
Lisa Faust, Ph.D.	Vice President, Lincoln Park Zoo	Conservation, Population Mgmt.
Paul Honess, Ph.D.	Director, Bioculture Group	Primate Behavior and Welfare
Sarah Long, M.S.	Director, Lincoln Park Zoo	Population Management
Elizabeth Lonsdorf, Ph.D.	Adjunct Scientist, Lincoln Park Zoo	Behavioral and Cognitive Research
Tetsuro Matsuzawa, D.Sc.	Director, Primate Research Institute	Primate Language and Intelligence
Steven Schapiro, Ph.D.	Section Chief, The University of Texas	Primate Environmental Enrichment
John L. VandeBerg, Ph.D.	Director, Southwest National Primate Research Cntr.	Genetics
Richard Wrangham, Ph.D.	Co-Director, Kibale Chimpanzee Project	Biological Anthropology
Stuart Zola, Ph.D.	Director, Yerkes Regional Primate Research Center	Psychiatry and Behavioral Sciences

Consultants to Working Group

Name	Title	Expertise
Bruce M. Altevogt, Ph.D.	Senior Program Officer Institute of Medicine	Neuroscience
Jeffrey P. Kahn, Ph.D., M.P.H.	Deputy Director Berman Institute of Bioethics, JHU	Bioethics and Public Policy
Jay R. Kaplan, Ph.D.	Director Wake Forest University Primate Center	Pathology – Comparative Medicine
Stanley Lemon, M.D.	Prof. of Medicine University of North Carolina at Chapel Hill	Infectious Diseases
Charles Rice, Ph.D.	Professor in Virology The Rockefeller University	Virology, Infectious Diseases
Robert Sapolsky, Ph.D.	Professor of Biological Sciences Stanford University	Neuroscience

Consultants—Emerging Diseases Subgroup

Name	Title	Expertise
L. Bill Cummins, D.V.M.	Special Assistant to the Director Southwest National Primate Research Center	Veterinary Science
Frederick A. Murphy, D.V.M., Ph.D.	Professor, Department of Pathology University of Texas	Virology, Pathology
Mark Slifka, Ph.D.	Professor Oregon Health & Science University	Microbiology and Immunology
LeeThompson	Assistant Professor (retired) University of Texas Medical Branch	Pathology

The Working Group Report

Report Organization

Executive Summary of the 28 Recommendations

Overview and Organization of the Report

Glossary of Terms Used

Section 1: NIH-Supported Chimpanzee Research and IOM Principles and Criteria

Section 2: Working Group on the Use of Chimpanzees in NIH-Supported Research

Section 3: Ethologically Appropriate Physical and Social Environments: A Key Concept in the IOM Principles **Section 4:** Review of Currently Active NIH-Supported Research Using Chimpanzees

Section 5: Size and Placement of Research-Active and Research-Inactive Populations of NIH-owned and NIHsupported Chimpanzees

Section 6: Review Process for Future Proposals to Use Chimpanzees in NIH-Supported Research

Section 7: Conclusion

References

Acknowledgements

Appendices A - G

Recommendations

Ethologically Appropriate Physical and Social Environments: A Key Concept in the IOM Principles (10 recommendations)

Review of Currently Active NIH-Supported Research Using Chimpanzees

Size and Placement of Research-Active and Research-Inactive Populations of NIH-owned and NIH-supported Chimpanzees (9 recommendations)

Review Process for Future Proposals to Use Chimpanzees in NIH-Supported Research (9 recommendations)

Ethologically Appropriate Physical and Social Environments: A Key Concept in the IOM Principles (10 recommendations)

1. Chimpanzees must have the opportunity to live in sufficiently large, complex, multi-male, multi-female social groupings, ideally consisting of at least 7 individuals. Unless dictated by clearly documented medical or social circumstances, no chimpanzee should be required to live alone for extended periods of time. Pairs, trios, and even small groups of 4 to 6 individuals do not provide the social complexity required to meet the social needs of this cognitively advanced species. When chimpanzees need to be housed in groupings that are smaller than ideal for longer than necessary, for example, during routine veterinary examinations or when they are introduced to a new social group, this need should be regularly reviewed and documented by a veterinarian and a primate behaviorist.

- The density of the primary living space of chimpanzees should be at least 1,000 ft² (93 m²) per individual. Therefore, the minimum outdoor enclosure size for a group of 7 animals should be 7,000 ft² (651 m²).
- 3. Chimpanzees must be housed in environments that provide outdoor access year round. They should have access to natural substrates, such as grass, dirt, and mulch, to enhance environmental complexity.
- 4. Chimpanzees should have the opportunity to climb at least 20 ft (6.1 m) vertically. Moreover, their environment must provide enough climbing opportunities and space to allow all members of larger groups to travel, feed, and rest in elevated spaces.

- Progressive and ethologically appropriate management of chimpanzees must include provision of foraging opportunities and of diets that are varied, nutritious, and challenging to obtain and process.
- 6. Chimpanzees must be provided with materials to construct new nests on a daily basis.
- 7. The environmental enrichment program developed for chimpanzees must provide relevant opportunities for choice and self-determination.

8. Chimpanzee management staff must include experienced and trained behaviorists, animal trainers, and enrichment specialists to foster positive human-animal relationships and provide cognitive stimulation. Given the importance of trainer/animal ratios in maintaining trained behaviors, a chimpanzee population of 50 should have at least 2 dedicated staff members with this type of expertise. Positive reinforcement training is the only acceptable method of modifying behaviors to facilitate animal care and fulfillment of management needs. Training plans should be developed for each animal, and progress toward achieving established benchmarks should be documented.

- 9. All personnel working with chimpanzees must receive training in core institutional values promoting psychological and behavioral well-being of chimpanzees in their care. These institutional core values should be publicly accessible.
- 10. Chimpanzee records must document detailed individual animal social, physical, behavioral, and psychological requirements and these requirements should be used to design appropriate individualized chimpanzee management in the captive research environment.

To Consider...

Ethologically appropriate environments

- Environments that meet the full range of physical, social, and management characteristics
- Should be available to house NIH-owned and NIH-supported research-active and research-inactive chimpanzees within 3 to 5 years

Ethologically inappropriate environments

- Environments where components of complexity and stimulation are not available
- Not acceptable for long-term housing
 - For example, the use of squeeze cages and frequent darting or tranquilization

Additional Considerations

Temporary housing conditions

- Defined by the Working Group as those needed to hold animals for between 24 hours to 21 days
- Might be necessary to conduct biomedical research that meets the IOM criteria but requires short-term containment
 - Examples: preventive health examinations and related sedation as well as noninvasive and voluntary cognitive testing

Transitional housing conditions

- Might be required for the next 3 to 5 years to accommodate chimpanzees until ethologically appropriate primary living spaces become available
- An interim solution, not intended for long-term housing of chimpanzees
- Strict 5-year time limit

Review of Currently Active NIH-Supported Research Using Chimpanzees

Summary of Projects Reviewed

- <u>Continue</u>: These projects comply with all IOM principles and criteria and the Working Group recommended that the NIH continue to support these projects until the end of the current project period.
- <u>End</u>: These projects do not comply with some or all of the IOM principles and criteria, and the Working Group recommended that the NIH phase out these projects in a way that preserves the value of the research already conducted and avoids an unacceptable impact on the animals.
- <u>Conditionally approved to continue</u>: One of the IOM principles is that the chimpanzees must be housed in an "ethologically appropriate" environment.
 - indicates that a currently active project may continue until the end of the current project period (e.g., next competitive renewal) but is not eligible for a no-cost-extension or other means to extend the original project term.

Working Group Recommendations on Currently Active Projects

		Working	Group Recommen	dations	
	Total Number of Projects Considered	Continue	Conditionally Approved to Continue	End	Recommendations
Biomedical research	9	0	3*	7*	 Conditionally approved to continue for 3 projects involving immunology and infectious agents End 6 projects
Comparative genomics and behavioral research	13	2**	7**	5	 Continue or conditionally approved to continue for 6 behavioral research and 2 comparative genomics/proteomics studies End 5 projects
Colony housing and care	8	0	7†	4†	 Conditionally approved to continue for 7 projects End 1 project and the research component of 3 conditionally approved projects

Asterisks indicate projects that received multi-part recommendations. See report for details.

Size and Placement of Research-Active and Research-Inactive Populations of NIH-owned and NIHsupported Chimpanzees (9 recommendations)

Census of NIH-Owned and NIH-Supported	NIH-Owned and	NIH-Supported but	
Research Chimpanzees at Research Facilities	Supported	NotOwned	Total
(research-active and research-inactive chimpanzees)			
Michala E. Kaaling Contar for Comparative Medicine and Pessarch. The			
University of Texas M.D. Anderson Cancer Center, Bastrop, TX	167	0	167
Southwest National Primate Research Center,	2.4	~1	11F
Texas Biomedical Research Institute, San Antonio, TX	24	91.	115
Total at Research Facilities	191	91	282
Research Chimpanzees at Research Reserve Facility			
(research-inactive)			
Alamogordo Primate Facility, Alamogordo, NM	169	0	169
Total Research Chimpanzees	360	91	451
Retired Chimpanzees			
Chimp Haven, Inc., Keithville, LA	109**	0	109
New Iberia Research Center,			
The University of Louisiana at Lafayette, New Iberia, LA	110***	0	110
Total Research and Retired Chimpanzees	579	91	670
Asterisks indicate the ownership and status of chimpanzee population. See report for correspondin	g footnotes.		33

Future Need for Chimpanzees in Research

- Using the criteria for biomedical and comparative behavioral and genomic research defined in the IOM report, the Working Group evaluated all projects currently funded by the NIH that involve chimpanzees.
 - The Working Group concluded that 6 of 9 biomedical research projects using 81 of 93 chimpanzees *did not* meet the IOM criteria.
 - The Working Group recommended ending these projects while ensuring that the scientific value of the research is preserved.
- The Working Group's recommendations regarding active NIH-funded biomedical research projects demonstrate that the need to use chimpanzees in invasive biomedical research has diminished substantially.

Future Need for Chimpanzees in Research

- The Working Group found it more difficult to determine the future need for minimally invasive research that inflicts little or no harm on chimpanzee subjects.
 - Currently, several investigators are using approximately 300 chimpanzees for comparative genomic and behavioral research.
 - The Working Group was able to conditionally approve to continue several projects involving comparative genomics or behavioral research involving 290 chimpanzees.

New, Emerging, and Reemerging Diseases

- Infectious disease research would warrant the use of chimpanzees only in unique and rare situations.
- Even for highly virulent Ebola and monkeypox viruses, significant research and human health advances have been achieved using smaller animal models.
- Chimpanzees do not play a role in discovery-phase infectious disease research, except in studies on a very small number of infectious agents (e.g., hepatitis viruses).
- In some very rare cases of research on infectious diseases that present an exceptional threat to public health, the theoretical possibility of needing to use chimpanzees in the highest biocontainment-level facilities exists.
 - However, none of the ABSL4 facilities in the United States is designed to accommodate chimpanzees

New, Emerging, and Reemerging Diseases

- There is no compelling scientific reason to maintain a sufficiently large reserve population of chimpanzees suitable and/or available for infectious disease research, even in the case of a national emergency.
- Alternative animal models (e.g., mice, rats, hamsters, guinea pigs, and other nonhuman primates) are currently and increasingly used and developed to study emerging infectious diseases.
 - The availability of these models will continually raise the scientific bar for justifying the use of chimpanzees.

- The majority of NIH-owned chimpanzees should be designated for retirement and transferred to the federal sanctuary system. Planning should start immediately to expand current facilities to accommodate these chimpanzees. The federal sanctuary system is the most speciesappropriate environment currently available and thus is the preferred environment for long-term housing of chimpanzees no longer required for research.
- 2. A small population of chimpanzees should be maintained for future potential research that meets the IOM principles and criteria. Based on an assessment of current research protocols and interviews with content experts and current research facility administrators, this colony is estimated to require approximately 50 chimpanzees. The size and placement of this colony should be reassessed on a frequent basis (approximately every 5 years) to ensure that such a colony is still actually needed and that the animals are not overused.

- 3. This small chimpanzee colony should be maintained at a facility that has the characteristics of ethologically appropriate physical and social environments described in the report. Thus, plans should be made now to ensure that ethologically appropriate physical and social housing conditions will be available within 3 to 5 years. Maintaining the chimpanzee colony at a single facility could be advantageous to minimize costs and maximize management flexibility.
- 4. The demographic constitution of this small chimpanzee colony is important to maximize its utility for research. Ideally, the colony should be age and sex stratified, have an approximately 50:50 sex ratio, and be composed primarily of animals that are healthy and younger than 30 years. At least half of this population should be physiologically naïve to infection (e.g., hepatitis or HIV). When this colony is formed, best practices should be used for maintaining current social groupings, whenever possible, to minimize adverse stress.

- 5. The NIH should review its funding priorities for comparative behavioral, cognitive, and genomic studies using chimpanzees. The NIH should consider targeting funding for low-burden projects that can be conducted in nontraditional research settings that can maintain ethologically appropriate environments or projects that use materials collected during routine veterinary examinations.
- 6. The NIH should not support any long-term maintenance of chimpanzees intended for research on new, emerging, or reemerging diseases in animal biosafety level 2 or greater biocontainment-level facilities.
- 7. The NIH should not, on its own, revitalize breeding strategies to derive a population of chimpanzees for any research, including for new, emerging, or reemerging disease research.

- 8. The NIH should collaborate with other federal agencies (i.e., Centers for Disease Control and Prevention and Food and Drug Administration) and departments (i.e., Department of Defense and Department of Homeland Security) when considering any future plan for placement, maintenance, and use of chimpanzees in research in response to a new, emerging, or reemerging disease that could represent a national security risk to the United States.
- 9. In light of evidence suggesting that research involving chimpanzees has rarely accelerated new discoveries or the advancement of human health for infectious diseases, with a few notable exceptions such as the hepatitis viruses, the NIH should emphasize the development and refinement of other approaches, especially alternative animal models (e.g., genetically altered mice), for research on new, emerging, and reemerging diseases.

Review Process for Future Proposals to Use Chimpanzees in NIH-Supported Research (9 recommendations)

Oversight Committee Composition

- 1. The NIH should replace the Interagency Animal Models Committee with an independent Oversight Committee Using Chimpanzees in NIH-Supported Research (Oversight Committee) to advise on the proposed use of chimpanzees in research. The current Interagency Animal Models Committee is not considered independent from other individuals and bodies that review and approve grant applications to the NIH, contains no members of the public, and thus does not fully meet the spirit of the IOM principles and criteria.
- 2. The Oversight Committee should be separate from extramural initial review groups, intramural scientific program personnel, and Institute or Center directors. In addition, the Oversight Committee's reviews should take place after the standard reviews and approvals by these entities. The Oversight Committee's reviews will focus on whether the proposed research is consistent with the IOM principles and criteria for the use of chimpanzees in research.

Oversight Committee Composition

3. The Oversight Committee should be comprised of individuals with the specific scientific, biomedical, and behavioral expertise needed to properly evaluate whether a grant, intramural program, contract, or other award mechanism supporting research using chimpanzees complies with the IOM principles and criteria.

Review Process

4. Investigators seeking NIH funding to conduct research using chimpanzees must explain in their application how their proposed research complies with the IOM principles and criteria. This supplemental information must address all of the questions posed in the decision-making algorithm in this report and provide sufficient detail for consideration by the Oversight Committee. This information is in addition to the vertebrate animal section and/or applicable animal study protocol. The NIH might wish to develop a form or other suggested template for investigators to use for this purpose.

Review Process

- 5. To ensure that the scientific use of chimpanzees is justified, the animal numbers and group sizes must be statistically justified before the NIH approves any proposed research project involving the use of chimpanzees.
- 6. Investigators need not include supplemental information on chimpanzee use for proposals involving the following, and these proposals will be exempt from Oversight Committee review:
 - The use of any biomaterials, including pathological specimens, collected and stored prior to submission of the research proposal or as part of a research grant or contract that has undergone Oversight Committee review and approval, or as part of regular veterinary (health) examinations;
 - Other observational or non-interventional studies, such as behavioral observations in the wild that do not result in contact or otherwise interfere with the chimpanzees being observed; or
 - Noninvasive collection of samples from the wild in a manner that does not result in contact or otherwise interfere with the chimpanzees during the collection.

Decision Tree (abbreviated – see report for details)



Decision Tree (abbreviated – see report for details)



Burden-Benefit Matrix

	Lowest or minimal	BURDEN More than minimal	High	
	Unlikely to meet criteria	Not acceptable	Not acceptable	
BENEFIT Moderate	Might meet criteria	Might meet criteria	Not acceptable	
High	Likely to meet criteria	Might meet criteria	Might meet criteria	

The determinations of the Oversight Committee that proposals (or parts of them) meet or do not meet the IOM principles and criteria should be transmitted to the Federal Advisory Committee Act committee assigned by the NIH Director to consider the Oversight Committee's determinations.

Placement of Oversight Committee Review

7. The Oversight Committee review should take place after the Center or Institute director approves a proposal so key elements of the review are publicly accessible to the extent allowable by federal regulations. The Oversight Committee should review all requests for grants, contracts, intramural projects, and third-party projects rather than establishing a separate review process for each mechanism. Funding of an award for research involving the use of chimpanzees that has received an Institute or Center director's approval will be conditional and subject to the subsequent evaluation by the Oversight Committee.

Placement of Oversight Committee Review

- 8. The Oversight Committee will base its reviews on the supplemental information provided by investigators on how the proposed research complies with the IOM principles and criteria and all relevant documents (including animal study protocols and grant applications) required to make informed determinations for all funding requests (grants, contracts, and intramural projects) and other requests to use chimpanzees (e.g., third-party projects).
- 9. The Oversight Committee will determine whether each application meets of does not meet the IOM principles and criteria based on votes of a majority of all voting members. At its members' discretion, the Oversight Committee may vote on whether different components or parts of an application meet or do not meet the IOM principles and criteria.

Next Steps...

Next Steps...

Working Group Report Considered by the CoC

NIH Issues a 6o-Day Request for Information

NIH Director to Review Comments

NIH Decision

NIH Implementation

52

Questions?

Thank You.