

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

**Report**

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## **Executive Summary**

This report summarizes the findings and recommendations of the Working Group on the Use of Chimpanzees in National Institutes of Health (NIH)-Supported Research. The NIH formed this committee within the Council of Councils, a federal advisory committee, to advise the NIH on the implementation of the recommendations of the Institute of Medicine's (IOM's) Committee on the Use of Chimpanzees in Biomedical and Behavioral Research regarding the use of chimpanzees in NIH-sponsored research. In December 2010, the NIH asked the IOM to review the current use of chimpanzees in NIH-funded biomedical and behavioral research that is needed to advance the public's health. The IOM committee focused its efforts on the nearly 700 chimpanzees owned or otherwise supported by the NIH.

In December 2011, the IOM committee completed its review, concluding that although the chimpanzee has been a valuable animal model in the past, most current biomedical use of chimpanzees is unnecessary. At the same time, the IOM committee concluded that chimpanzees could still serve an important role in some areas of research but in these areas, the research must be governed by a set of principles and criteria. These principles and criteria address the necessity of the research for answering important public health questions, the need to use the chimpanzee model to answer these questions, and whether the chimpanzee-housing and the research conditions are appropriate for humans' closest relative.

The NIH immediately accepted the IOM committee's principles and criteria and assembled the Working Group on the Use of Chimpanzees in NIH-Supported Research in February 2012. The NIH charged the Working Group in February 2012 with:

- 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.

On January 22, 2013, the Working Group delivered its report and recommendations to the NIH Council of Councils. The Working Group's recommendations are listed below. The body of this report provides background information on all of these issues.

### **Ethologically Appropriate Physical and Social Environments: A Key Concept in the IOM Principles**

Throughout its report, the IOM committee used the term "ethologically appropriate physical and social environments" as a central principle for how chimpanzees used in research should be housed. Because the IOM report did not provide further details, the Working Group first defined

the term “ethologically appropriate physical and social environments” as environments that not only *allow*, but importantly, *promote* the full range of natural chimpanzee behaviors. The Working Group then used this definition to make recommendations concerning the placement of research chimpanzee populations.

The Working Group’s recommendations with respect to ethologically appropriate physical and social environments are as follows:

**Recommendation EA1:** 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.

\*In this context, the Working Group defines a “veterinarian” as a licensed, graduate veterinarian with demonstrated expertise in the clinical care and welfare of nonhuman primates (preferably chimpanzees) and who is directly responsible for the routine clinical care of the animal(s) in question.

**Recommendation EA2:** The density of the primary living space of chimpanzees should be at least 1,000 ft<sup>2</sup> (93 m<sup>2</sup>) per individual. Therefore, the minimum outdoor enclosure size for a group of 7 animals should be 7,000 ft<sup>2</sup> (651 m<sup>2</sup>).

**Recommendation EA3:** 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.

**Recommendation EA4:** 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.

**Recommendation EA5:** 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.

**Recommendation EA6:** Chimpanzees must be provided with materials to construct new nests on a daily basis.

**Recommendation EA7:** The environmental enrichment program developed for chimpanzees must provide relevant opportunities for choice and self-determination.

**Recommendation EA8:** 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.

**Recommendation EA9:** 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.

**Recommendation EA10:** 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.

### **Chimpanzee Research Colony Size and Placement**

The Working Group's charge included advising the NIH on the size and placement of NIH-owned and NIH-supported research-active and research-inactive chimpanzee populations. The Working Group's recommendations with respect to colony size and placement, including whether additional chimpanzees are needed for research to prepare for new, emerging, and reemerging diseases, are as follows:

**Recommendation SP1:** 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 species-appropriate environment currently available and thus is the preferred environment for long-term housing of chimpanzees no longer required for research.

**Recommendation SP2:** 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.

**Recommendation SP3:** This small chimpanzee colony should be maintained at a facility that has the characteristics of ethologically appropriate physical and social environments described in this 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.

**Recommendation SP4:** 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.

**Recommendation SP5:** The NIH should review its funding priorities for comparative behavioral, cognitive, and genomics 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.

**Recommendation SP6:** 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.

**Recommendation SP7:** 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.

**Recommendation SP8:** 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.

**Recommendation SP9:** 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**

Part of the Working Group's charge was to advise on a review process for considering whether the potential future use of chimpanzees in NIH-supported research is scientifically necessary and consistent with the IOM principles. The Working Group's recommendations regarding the establishment of an independent oversight committee and review process are as follows:

## Oversight Committee Independence and Expertise

**Recommendation RP1:** The NIH should replace the Interagency Animal Models Committee with an independent Oversight Committee for Proposals 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.

**Recommendation RP2:** 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.

**Recommendation RP3:** 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

**Recommendation RP4:** 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.

**Recommendation RP5:** 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.

**Recommendation RP6:** 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/or 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.

#### Placement of Oversight Committee Review

**Recommendation RP7:** The Oversight Committee review should take place after the Center or Institute director approves a proposal so that the 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.

**Recommendation RP8:** 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).

**Recommendation RP9:** The Oversight Committee will determine whether each application meets or does not meet the IOM principles and criteria based on the 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.

## Overview and Organization of the Report

This report provides two brief introductory sections and four chapters that address the charge of the Working Group on the Use of Chimpanzees in National Institutes of Health (NIH)-Supported Research.

- Section 1 provides background information on the use of chimpanzees in NIH-supported research and introduces the principles and criteria of the Institute of Medicine's (IOM's) Committee on the Use of Chimpanzees in Biomedical and Behavioral Research.
- Section 2 describes the creation, charge, and activities of the Working Group.
- Section 3 describes the process that the Working Group used to develop an implementation plan for the IOM principles and criteria and defines the term "ethologically appropriate physical and social environments," a key term used in the IOM principles and throughout this report.
- Section 4 offers the Working Group's recommendations regarding the future of currently funded research projects using chimpanzees.
- Section 5 addresses the number of chimpanzees that might be needed for NIH-funded research in the future and the placement of these animals. This section also addresses whether chimpanzees are likely to be needed to study new, emerging, and reemerging diseases.
- Section 6 provides recommendations and implementation guidance pertaining to the review process for considering whether the potential future use of chimpanzees in NIH-supported research is scientifically necessary and consistent with the IOM principles and criteria.

In some cases, the Working Group made specific recommendations regarding critical aspects of chimpanzee environments. The Working Group developed these quantitative recommendations using a range of inputs, including Working Group members' expertise, interviews of experts with knowledge of wild and captive chimpanzees, published information about the behavior of wild and captive chimpanzees, and consideration of practical constraints pertaining to chimpanzee management and facilities.

This overview is followed by a glossary of terms used in this report. The appendices include the Working Group member roster and biographies; list of consultants; schedule of Working Group activities; summary of expert interviews conducted by the Working Group; summary of public input in response to NIH requests for information on the use of chimpanzees in research; and a white paper on the use of chimpanzees for research on new, emerging, and reemerging diseases.

## Glossary of Terms Used in this Report

**Acquiescence:** voluntary participation in an activity based solely on positive reinforcement training and not involving forced participation or engagement by coercion. According to this definition, animals choose whether to participate or not based on their own volition.

**Behavioral research:** research that involves the study of overt actions; underlying psychological processes such as cognition, emotion, temperament, and motivation; and biobehavioral interactions.

**Biomedical research:** a broad area of science that seeks ways to prevent and treat diseases that cause illnesses and death in people and in animals. Biomedical researchers study biomedical processes and diseases with the ultimate goal of developing effective treatments and cures.

**Chimpanzee Health Improvement Maintenance and Protection (CHIMP) Act:** an act, signed by the President on December 20, 2000, to amend the Public Health Service Act to provide for a system of sanctuaries for retired chimpanzees that are no longer needed in federally funded research.

**Chimp Haven is Home Act:** an act, signed by the President on December 26, 2007, to amend the Public Health Service Act and modify the CHIMP Act by terminating the authority to remove retired chimpanzees from the sanctuary system for research purposes.

**Committee on the Use of Chimpanzees in Biomedical and Behavioral Research (also referred to as “IOM Committee”):** committee formed by the IOM and the National Research Council to review the current use of chimpanzees in NIH-funded biomedical and behavioral research that is needed for the advancement of the public’s health.

**Comparative genomics:** a field of biological research in which the genome sequences of different species (such as humans, mice, and chimpanzees) are compared. These comparisons allow researchers to identify regions of similarity and difference, shedding light on the structure and function of human genes and supporting the development of new strategies to combat human disease.

**Council of Councils:** a federal advisory committee established by the NIH Reform Act of 2006, passed by Congress in December 2006 and signed into law by the President in January 2007. The Council advises the NIH Director and other delegated officials on matters related to the policies and activities of the Division of Program Coordination, Planning, and Strategic Initiatives.

**Culture of care:** concept embraced by the Working Group that should be promoted in ethologically appropriate environments. In a culture of care, chimpanzees are managed in a manner that engenders respect and mutually positive human-animal relationships.

**Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI):** a component of the NIH whose mission is to identify emerging scientific opportunities, rising

public health challenges, and scientific knowledge gaps that merit further research. DPCPSI oversees the NIH Chimpanzee Management Program.

**Emerging diseases:** include outbreaks of previously unknown infectious diseases or known diseases whose incidence or geographic range is increasing in humans.

**Ethologically appropriate physical and social environments (also referred to as “ethologically appropriate environments”):** captive environments that do not simply allow but also, importantly, promote a full range of behaviors that are natural for chimpanzees.

**Ethologically inappropriate environments:** environments that do not provide the complexity and stimulation that chimpanzees need, such as environments that house smaller groups of animals and have only moderate complexity or in which chimpanzees are managed through the use of squeeze cages and frequent darting or tranquilization for holding or experimental purposes.

**Federal sanctuary system:** the sanctuary system created in compliance with the CHIMP Act to provide lifetime care for federally owned retired chimpanzees that are no longer needed for research.

**Institute of Medicine (IOM):** an independent, nonprofit organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public.

**Interagency Animal Models Committee:** chartered by the NIH in 1989 to provide oversight of all federally supported biomedical and behavioral research involving chimpanzees.

**Invasive research:** according to the Standards for a National Chimpanzee Sanctuary System, research that causes more than momentary pain, distress, fear, discomfort, injury, or other negative modalities to a chimpanzee, including any procedure that enters or exposes a body cavity.

**Minimally invasive research:** any research that inflicts little or no harm and that minimizes pain and distress.

**National Institutes of Health (NIH):** an agency of the U.S. Department of Health and Human Services that is the primary U.S. government agency responsible for biomedical and health-related research.

**National Primate Research Centers (NPRCs):** provide facilities, animals, and expertise for investigators using nonhuman primates for biomedical research. NPRCs are supported in part by the NIH.

**New, emerging, and reemerging diseases:** new infectious diseases or diseases of infectious origin whose incidence in humans has increased within the past two decades or threatens to increase in the near future.

**NIH-owned chimpanzees:** chimpanzees directly owned by the NIH.

**NIH-supported chimpanzees:** chimpanzees not owned by the NIH but supported through NIH awards, such as grants and contracts.

**Nonhuman primates:** all nonhuman members of the order Primates, including monkeys, chimpanzees, orangutans, gorillas, gibbons, apes, baboons, marmosets, tamarins, lemurs, and lorises.

**Noninvasive research:** research that involves minimal physical and mental harm, pain, distress, and disturbance to the chimpanzee and the social group in which the chimpanzee lives.

**Reemerging diseases:** known diseases that have reappeared after a significant decline in incidence.

**Research-active chimpanzees:** NIH-owned or -supported chimpanzees used for current research projects.

**Research-inactive chimpanzees:** NIH-owned or -supported chimpanzees not currently used for research but that might be used for new projects that meet the IOM principles and criteria.

**Retired chimpanzees:** chimpanzees that live permanently in the federal sanctuary system and cannot be removed from that system.

**Temporary housing conditions:** conditions needed to hold animals for between 24 hours and 21 days, such as standard indoor-outdoor run cages, outdoor geodesic housing structures, and small outdoor corrals.

**Transitional housing conditions:** an interim solution that is not intended for long-term housing of chimpanzees under any circumstance and should only be approved after detailed plans for achieving ethologically appropriate physical and social environment conditions have been formalized.

**Veterinarian:** a licensed, graduate veterinarian with demonstrated expertise in the clinical care and welfare of nonhuman primates (preferably chimpanzees) and who is directly responsible for the routine clinical care of the animal(s) in question.

**Working Group on the Use of Chimpanzees in NIH-Supported Research:** created on February 1, 2012, within the Council of Councils of the NIH and charged to provide advice on the implementation of the principles and criteria in the IOM report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*.

## **Section 1. NIH-Supported Chimpanzee Research and Institute of Medicine Principles and Criteria**

The National Institutes of Health (NIH), part of the U.S. Department of Health and Human Services, is the nation's medical research agency. The mission of the NIH is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. To fulfill this mission, the NIH sponsors research throughout the world and in its own laboratories.

Some research activities supported by the NIH involve the use of animal models to study important biomedical and/or behavioral conditions, and the agency devotes additional resources to caring for and housing animals used in research. The use of animals in research has enabled scientists to identify new ways to treat illness, extend life, and improve health and well-being.

### **NIH-Supported Research Involving Chimpanzees**

In limited circumstances, the NIH has funded research involving chimpanzees. Chimpanzees' close genetic proximity to humans makes them a uniquely valuable species for studying certain human conditions; they have provided exceptional insights into human biology and behavior. For example, this research has:

- Contributed significantly to the development of the hepatitis A and B vaccines in use today. These vaccines are usually given to children and, since 1991, the number of hepatitis B cases in children under age 15 years has declined by 98 percent. The rate of new hepatitis A infections in the United States dropped by more than 92 percent between 1995 and 2008.
- Identified the hepatitis C virus, which has led to improved public health measures, increased the safety of blood donations, and led to the development of emerging therapies (Choo et al. 1989).
- Determined that dietary salt is a major causative factor in elevated blood pressure (Denton et al., 1995).
- Developed monoclonal antibodies approved by the U.S. Food and Drug Administration for use in treating lymphomas and other cancers and establishing that certain in vitro differentiated immune cells can serve as vehicles for cancer immunotherapy (Larsson et al., 2004).

NIH-funded research involving chimpanzees has ranged from studies of infectious agents, hepatitis, and HIV/AIDS to studies of learning, cognition, and mental health conditions. Today, however, new methods and technologies developed by the biomedical community have provided alternatives to the use of chimpanzees in several areas of research.

Except for brief surges in research to explore new hypotheses, the NIH estimates that researchers proposed using approximately 100 chimpanzees for biomedical research sponsored by the NIH each year, on average, throughout the 1990s. The average number proposed for biomedical research increased to approximately 200 chimpanzees per year in the 2000s. For behavioral research, the NIH estimates that researchers proposed using slightly more chimpanzees than for biomedical research during these periods.

Although the NIH funds more chimpanzee research than any other federal agency, only a very small proportion—less than one tenth of one percent—of active NIH projects involve chimpanzees as of January 22, 2013. In a recent review of awarded projects involving chimpanzees, the NIH identified 30 projects that were actively using chimpanzees between May and December 2012. These projects involved biomedical, behavioral, or comparative genomics research using chimpanzees or used NIH funds to pay for the care and housing of chimpanzees. Additional details about these projects are available in Section 4 of this report.

### **Committee on the Use of Chimpanzees in Biomedical and Behavioral Research**

Members of the public, Congress, and some scientists have inquired about the continued need for the NIH to sponsor biomedical and behavioral research that uses chimpanzees. Some contend, for example, that chimpanzees are not suitable models in many cases for studies of human disease or that research can accomplish its aims without using this animal model (Institute of Medicine [IOM], 2011). However, other experts point out that research using chimpanzees has made critical contributions to public health, including the development of the Sabin polio vaccine and the identification of the hepatitis C virus, and this research is necessary to improve our understanding of certain diseases and conditions (*Nature*, 2011).

In December 2010, U.S. Senators Jeff Bingaman (D-NM), Tom Harkin (D-IA), and Tom Udall (D-NM) asked the National Academies to analyze the current and future need for the use of chimpanzees in biomedical research. That same month, the NIH commissioned a study by the IOM of the National Academies to assess whether chimpanzees are or will be necessary for biomedical and behavioral research.

In response to the NIH request, the IOM collaborated with the National Research Council to form the Committee on the Use of Chimpanzees in Biomedical and Behavioral Research (IOM committee). The IOM committee's task was to review the current use of chimpanzees in NIH-funded biomedical and behavioral research that is needed for the advancement of the public's health.

To accomplish its task, the committee was to (IOM, 2011, p. 13):

- *Explore contemporary and anticipated biomedical research questions to determine if chimpanzees are or will be necessary for research discoveries and to determine the safety and efficacy of new prevention or treatment strategies. If biomedical research questions are identified:*
  - *Describe the unique biological/immunological characteristics of the chimpanzee that made it the necessary animal model for use in the types of research;*
  - *Provide recommendations for any new or revised scientific parameters to guide how and when to use these animals for research; and*
- *Explore contemporary and anticipated behavioral research questions to determine if chimpanzees are necessary for progress in understanding social, neurological, and behavioral factors that influence the development, prevention, or treatment of disease.*

## 2011 IOM Report: Principles and Criteria

In addressing its task, the IOM committee explored contemporary and anticipated future alternatives to the use of chimpanzees in biomedical and behavioral research that will be needed for the advancement of the public's health. The committee collected information for its analysis by holding three 2-day meetings, including two public information-gathering sessions. In addition, the committee met by conference call, solicited public comments, examined the current availability and use of chimpanzees, and reviewed the scientific literature.

The IOM issued a report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*, summarizing the committee's findings on December 15, 2011 (IOM, 2011). In its 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 (IOM, 2011, pp. 26–27):

1. *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 committee developed separate sets of criteria for assessing the necessity of using chimpanzees for biomedical research and for comparative genomics and behavioral research:

Biomedical research (IOM, 2011, pp. 67–68): *The National Institutes of Health should limit the use of chimpanzees in biomedical research to those studies that meet the following three criteria:*

1. *There is no other suitable model available, such as in vitro, nonhuman in vivo, or other models, for the research in question; and*
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.*

Comparative genomics and behavioral research (IOM, 2011, p. 69): *The National Institutes of Health should limit the use of chimpanzees in comparative genomics and behavioral research to those studies that meet the following two criteria:*

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 committee concluded that “*while the chimpanzee has been a valuable animal model in past research, most current use of chimpanzees for biomedical research is unnecessary*” (IOM, 2011, pp. 66–67). However, the IOM 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 committee was unable to reach consensus on the necessity of using chimpanzees to develop a prophylactic hepatitis C virus vaccine. Although the committee encouraged the NIH to continue to develop non-chimpanzee models and technologies, it acknowledged that new, emerging, and reemerging diseases could present challenges that might require the use of chimpanzees.

### **NIH Response to the IOM Report and Creation of the Working Group**

On December 15, 2011, Francis S. Collins, M.D., Ph.D., Director of the NIH, accepted the IOM committee recommendations and announced that the NIH was developing a plan for implementing the IOM committee’s guiding principles and criteria.<sup>1</sup> On December 21, 2011, Dr. Collins announced that the NIH would not fund any new or other competing projects (renewals and revisions) for research involving chimpanzees and would not allow any new projects to go forward with chimpanzees<sup>2</sup> until the NIH issues further policy implementing the IOM’s recommendations. The NIH subsequently clarified that the NIH would accept for peer review competing applications proposing the use of samples obtained from chimpanzees on or before December 15, 2011—the date on which the NIH accepted the IOM committee’s recommendations.<sup>3</sup> The NIH released this clarification in response to investigator concerns that the NIH policy might prohibit investigators from using stored samples from chimpanzees in research—an area of research that the IOM committee explicitly exempted from its criteria.

In addition, as part of its plan for implementing the IOM committee’s guiding principles and criteria, the NIH created the Working Group on the Use of Chimpanzees in NIH-Supported Research within the NIH Council of Councils on February 1, 2012. The NIH Council of Councils provides advice to the NIH Director and other appropriate delegated officials on matters related to the policies and activities of the Division of Program Coordination, Planning, and Strategic Initiatives. The Division oversees the NIH Chimpanzee Management Program.

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<sup>1</sup> Statement by NIH Director Dr. Francis Collins on the Institute of Medicine report addressing the scientific need for the use of chimpanzees in research: <http://www.nih.gov/news/health/dec2011/od-15.htm>.

<sup>2</sup> National Institutes of Health. NOT-OD-12-025: NIH Research Involving Chimpanzees: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-025.html>

<sup>3</sup> National Institutes of Health. NOD-OD-12-116, Clarification to the Interim Agency Policy, NIH Research Involving Chimpanzees: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-116.html>

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

### Working Group Charge

On February 2, 2012, the NIH charged the Working Group on the Use of Chimpanzees in NIH-Supported Research to provide advice on the implementation of the recommendations made by the IOM committee in its report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (IOM, 2011). The NIH asked the Working Group to prepare a report for consideration by the Council of Councils addressing the following elements of the Working Group's charge:

- 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<sup>4</sup>;
- 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.

### Working Group Leadership and Subgroups

#### Co-Chairs and Members

The NIH selected two members of the Council of Councils, Daniel H. Geschwind, M.D., Ph.D., and K.C. Kent Lloyd, D.V.M., Ph.D., to serve as co-chairs of the Working Group and oversee all Working Group activities. In consultation with the co-chairs, the NIH selected members of the Working Group with expertise in research involving chimpanzees, chimpanzee behavior and conservation, veterinary medicine, infectious diseases, and biomedical ethics. The Working Group's membership roster, member biographies, and consultants roster are available in Appendix A, Appendix B, and Appendix C, respectively.

Lists of the Working Group's meetings and field trips are available in Appendix D. At least one NIH employee attended all Working Group meetings.

#### Subgroups

The Working Group created four subgroups, described in Table 1, to fulfill its charge. Three of the subgroups consisted only of Working Group members. Due to the highly specialized topics

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<sup>4</sup> The Working Group has not participated in any NIH decisions regarding funding of grants, contracts, or other awards.

addressed by the Emerging Diseases Subgroup, that subgroup sought input from expert consultants. The Colony Management Subgroup interviewed experts on ethologically appropriate environments and on the size and placement of chimpanzees (see list of experts interviewed and a summary of interviews in Appendix E). The Colony Management, Emerging Diseases, and Process Review subgroups prepared draft documents summarizing their deliberations and recommendations. All Working Group members reviewed these documents, and this report incorporates final versions of these documents.

**Table 1: Subgroups of the Working Group on the Use of Chimpanzees in NIH-Supported Research**

<b>Subgroup</b>	<b>Members and/or Consultants</b>	<b>Responsibilities</b>
Colony Management Subgroup	Beatrice Hahn, M.D. Daniel Povinelli, Ph.D. <sup>5</sup> Stephen Ross, Ph.D. Patricia Turner, M.Sc., D.V.M., D.V.Sc.	<ul style="list-style-type: none"> <li>• Evaluate and make recommendations on the size and placement of colonies of chimpanzees</li> <li>• Draft recommendations on the IOM’s principles regarding “ethologically appropriate environments” for chimpanzees</li> </ul>
Emerging Diseases Subgroup	Alan Barrett, Ph.D. L. Bill Cummins, D.V.M. <sup>6</sup> Frederick A. Murphy, D.V.M., Ph.D. <sup>6</sup> Mark Slifka, Ph.D. <sup>6</sup> Lee Thompson <sup>6</sup>	<ul style="list-style-type: none"> <li>• Determine whether the use of chimpanzees is necessary to study emerging diseases or develop medical countermeasures</li> <li>• Identify the circumstances under which chimpanzees should be used for emerging disease research</li> </ul>
Process Review Subgroup	Daniel Povinelli, Ph.D. R. Alta Charo, J.D. Daniel H. Geschwind, M.D., Ph.D.	<ul style="list-style-type: none"> <li>• Evaluate whether one set of metrics/standards could be developed for both biomedical and behavioral/cognitive studies involving chimpanzees</li> <li>• Assess and make recommendations regarding the process for determining the future need to use chimpanzees in research</li> </ul>
Project Review Subgroup	All Working Group members	<ul style="list-style-type: none"> <li>• Review active NIH research involving chimpanzees</li> <li>• Advise on the process for closing studies that do not comply with IOM recommendations</li> </ul>

<sup>5</sup> From February to September 2012 only

<sup>6</sup> External expert

## Timeline of Major Activities

The timeline for the creation of the Council of Councils Working Group on the Use of Chimpanzees in NIH-Supported Research and its major activities is provided in Table 2.

**Table 2. Timeline of Creation of Working Group and Major Working Group Activities**

Activity	Date
Council of Councils approves creation of the Working Group	February 1, 2012
The NIH officially charges the Working Group	February 2, 2012
The NIH publishes requests for information in the NIH Guide for Grants and Contracts and the <i>Federal Register</i>	February 10 and February 23, 2012, with responses due by April 10, 2012
Working Group provides updates to Council of Councils	June 5, 2012 September 5, 2012 October 29, 2012 January 8, 2013
Working Group presents its final report to the Council of Councils	January 22, 2013

### Public Input

To inform the deliberations of the Working Group, the NIH issued two requests for information (RFIs) seeking public input on issues pertaining to the NIH's implementation of the IOM committee recommendations. The NIH published the RFIs in the NIH Guide for Grants and Contracts<sup>7</sup> on February 10, 2012 and in the *Federal Register*<sup>8</sup> on February 23, 2012. In these notices, the NIH asked for recommendations regarding the core areas of the Working Group's charge. The NIH received 110 comments in response to the two RFI notices. A summary of the comments is available in Appendix F. The Working Group members reviewed the responses to the RFI notices and took them into consideration when they developed the recommendations in the current report.

### Updates to the Council of Councils

The Working Group co-chairs provided four updates to the Council of Councils between February 2012 and January 2013. During the publicly open sessions on June 5, 2012, and September 5, 2012, the Council of Councils assessed the Working Group's progress and offered feedback. The co-chairs delivered additional updates during closed sessions on September 5, 2012, October 29, 2012, and January 8, 2013, to provide Working Group recommendations on currently awarded research projects involving chimpanzees. The Working Group's recommendations regarding these projects are summarized in Section 4 of this report.

<sup>7</sup> Request for Request for Information (RFI): Input into the Deliberations of the Council of Councils Working Group on the Use of Chimpanzees in NIH-Supported Research: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-052.html>

<sup>8</sup> Request for Request for Information (RFI): Input into the Deliberations of the Council of Councils Working Group on the Use of Chimpanzees in NIH-Supported Research: <http://www.gpo.gov/fdsys/pkg/FR-2012-02-23/pdf/2012-4269.pdf>

## **Section 3. Ethologically Appropriate Physical and Social Environments: A Key Concept in the IOM Principles**

### **Background**

A key component of the Working Group's charge was developing a plan to implement the IOM committee's principles and criteria. This effort involved convening subgroups with appropriate expertise to fulfill the Working Group's charge (described in Section 2 above), identifying subgroup responsibilities (also described in Section 2), and identifying key questions that needed to be answered to fully address the charge and to enable the NIH to implement the IOM committee's principles and criteria.

One of the key questions that the Working Group identified was how to define the term "ethologically appropriate physical and social environments," which the IOM committee used in its guiding principles. This term lacked generally accepted definitions in the IOM report and other literature. The Working Group therefore identified the characteristics of ethologically appropriate social environments and ethologically appropriate physical environments to develop a definition of "ethologically appropriate physical and social environments." This section describes the process that the Working Group used to identify those characteristics, its definition of "ethologically appropriate physical and social environments," and recommendations to assist the NIH in operationalizing this concept. This section also addresses additional issues related to captive environments, including chimpanzee management, the distinctions between ethologically appropriate and inappropriate environments, and temporary and transitional housing.

### **Ethologically Appropriate Physical and Social Environments for Captive Chimpanzees**

In its 2011 report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*, the Committee on the Use of Chimpanzees in Biomedical and Behavioral Research indicated that chimpanzees used in research should be maintained in either ethologically appropriate physical and social environments or in natural habitats, based on the goal of imposing "*minimal physiological and psychological harm to the animals*" (IOM, 2011, p. 28).

The IOM committee suggested that certain environments for chimpanzees accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International would be suitable for future housing of chimpanzees being maintained for research purposes. However, neither the IOM committee nor any other agency—including the Association of Zoos and Aquariums, Council of Europe, and the U.S. National Research Council—has defined the concept of an ethologically appropriate physical and social environment for captive chimpanzees.

The Working Group was charged with advising the NIH on how to implement the IOM committee's recommendations. The Working Group therefore needed to provide a working definition of ethologically appropriate physical and social environments for chimpanzees referred to in the IOM principles pertaining to the future use of chimpanzees in biomedical and comparative genomic and behavioral research.

The Working Group concluded that a captive environment can be considered ethologically appropriate when it does not simply allow but also, importantly, promotes a full range of behaviors that are natural for the species. In the tradition of modern ethology, the behavioral repertoire of free-ranging wild chimpanzees is used as the model, or gold standard, toward which facility management should aspire when developing captive environments.

The application of ethologically appropriate conditions to the maintenance of captive chimpanzees is further complicated by the fact that this Working Group report deals solely with chimpanzees maintained in captivity for research purposes. Although captive chimpanzees that are permanently retired and unavailable for research might well be maintained in ethologically appropriate physical and social environments, the NIH asked the Working Group to provide advice only on conditions for chimpanzees actively engaged in research protocols and for chimpanzees that are research inactive, or not currently participating in research.

The Working Group promotes a holistic and performance-based approach to creating an ethologically appropriate environment for captive chimpanzee management. Defining the full range of physical and social components that are critical for chimpanzee well-being would be challenging, and generating definitive, empirically based data for each program element would be nearly impossible. Thus, the Working Group's intent is to provide a framework for all significant parameters that constitute an ethologically appropriate physical and social environment for captive chimpanzees. In addition to physical and social characteristics, these parameters include factors related to animal management.

The environment and behavior of wild chimpanzees must be understood before determining how to recapitulate the most important aspects of the natural behavioral repertoire of chimpanzees in captive settings. The following subsections describe the environmental and behavioral features of chimpanzees' natural habitat along with the Working Group's recommendations based on these features.

## **Social Environments**

The most critical component of ethologically appropriate physical and social environments is the social environment. Chimpanzees in the wild live in large fission-fusion communities of up to 150 individuals, and constantly changing smaller subgroups of individuals break off and periodically rejoin the primary group (Wrangham, 1979; Goodall, 1986; Chapman et al., 1995). A core of adult males, which form the primary hierarchical structure of the community, dominates these groups. A less well-defined hierarchy exists among females (Pusey et al., 1997). Wild chimpanzee communities are composed of mixed-sex, mixed-age groups of related and unrelated individuals, with a range of inter-animal relationships. All of the animals in each group are familiar with one another. Chimpanzees' social systems are more complex and dynamic than those of most primates. These social systems are likely the basis for many of the high-level cognitive and behavioral complexities that have evolved in this species (Humphrey, 1976; Dunbar, 1998; reviewed in Hopper et al., 2012).

It is impossible to recreate the full and dynamic complexity of the social environment of wild chimpanzees. However, some sanctuaries have had considerable success in forming large, stable

social groups of more than 25 individuals. These groups almost always have a strong multi-male hierarchy. Although this hierarchy is variable over time, it makes up the long-term leadership structure in the group.

The degree to which a dynamic fission-fusion system is possible in research settings is unclear; however, important elements of fission-fusion social grouping have been successfully replicated. Captive environments that provide opportunities for clusters of animals to completely separate themselves spatially from others are essential. These features allow individuals to better self-regulate daily social and “political” interactions. In addition, multiple groups have been maintained at a single facility, with management facilitating regular inter-mixing of groups to replicate fission-fusion society. Whether implemented on a smaller scale (in-group separation) or in the context of larger, multi-group socialization (management-facilitated mixing), the functional elements of social choice are not only practically viable but are also highly desirable and necessary for creating an ethologically appropriate social environment for chimpanzees.

**Recommendation EA1:** 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.

\* In this context, the Working Group defines a “veterinarian” as a licensed, graduate veterinarian with demonstrated expertise in the clinical care and welfare of nonhuman primates (preferably chimpanzees) and who is directly responsible for the routine clinical care of the animal(s) in question.

## **Physical Environments**

The natural habitat of wild chimpanzees in equatorial Africa consists primarily of densely forested jungle, although some topographical variation exists. Chimpanzees spend approximately half their day off the ground (as high as 66 ft [20 m]), foraging within forest canopies for food and other resources (Doran, 1996). Daily travel is an essential aspect of chimpanzee life and the average home range extends from 4 miles (7 km) to more than 12 miles (20 km) (Nishida, 1987; Newton-Fisher, 2003). Food acquisition is not the only motivation for ranging because adult males spend considerable time patrolling the borders of their extensive territories to prevent intrusion from neighboring, unrelated chimpanzee communities (Mitani and Watts, 2005). Thus, natural chimpanzee environments are expansive and composed of a variety of foliage, substrates, and assorted topography, all of which provide a wide range of behavioral and locomotor opportunities.

Even the most ambitious captive environments are unlikely to achieve the sheer size and complexity of the natural African chimpanzee environment. The key aspects of natural habitats that represent critical components of an ethologically appropriate physical environment for this

species include space, climate, and height of the primary living space (defined as the environment with which chimpanzees have direct and immediate contact).

Extant research suggests that providing opportunities for captive chimpanzees to form subgroups and choose potential social partners is important (Clark, 2011) and that large and complex spaces facilitate species-typical behaviors (Bowen, 1980; Clarke et al., 1982; Aureli and de Waal, 1997; Videan and Fritz, 2007; Ross et al., 2010; Ross et al., 2011). The space available to captive chimpanzees should be large enough to support their complex social structures and sufficiently dense to allow functional subgrouping behaviors. More specifically, spaces should be large enough for chimpanzees to demonstrate their natural tendencies to range, travel, patrol, and separate from their social group completely when necessary.

**Recommendation EA2:** The density of the primary living space of chimpanzees should be at least 1,000 ft<sup>2</sup> (93 m<sup>2</sup>) per individual. Therefore, the minimum outdoor enclosure size for a group of 7 animals should be 7,000 ft<sup>2</sup> (651 m<sup>2</sup>).

The climate should be amenable to year-round outdoor access by animals. Although natural habitats of wild chimpanzees vary to some degree in temperature, humidity, and precipitation, this variability is considerably less than that of most temperate regions in North America. Ample evidence also suggests that providing outdoor access to chimpanzees confers significant behavioral benefits (Videan et al., 2005; Baker and Ross, 1998).

Similarly, captive environments should recapitulate, as much as possible, the complexity of natural environments to stimulate the full range of foraging, ranging, manipulation, tool-use, and socio-cultural behaviors of wild chimpanzees (Pruetz and McGrew, 2001). Natural outdoor environments are not recommended for aesthetics or rote replication of chimpanzee habitat. Rather, climate represents an important element of the natural, outdoor environments in which this species evolved and is also important for animal health (McGrew et al., 1981).

**Recommendation EA3:** 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.

Physical environments should be constructed to fully accommodate the natural arboreal nature of the species. Wild chimpanzees spend approximately half their waking hours above the ground foraging, nesting, ranging, and interacting. Captive chimpanzees show a clear preference for elevated spaces, preferentially selecting them over areas that are closer to the ground (Traylor-Holzer and Fritz, 1985; Goff et al., 1994; Ross and Lukas, 2006; Ross et al., 2011). Although an artificial, constructed climbing apparatus can replicate the functionality of these behavior patterns, a natural forest habitat provides additional important elements, including shade, foraging opportunities, visual hides, and humus and other forms of natural ground cover. Artificial structures cannot fully replicate these variable and complex environmental elements, especially for the range and size of the spaces described. Thus, ethologically appropriate environments are large enough to provide sufficient opportunities to range, form subgroups, and travel. Ideally, these environments are composed of natural substrates, including forests and other terrains, to replicate the complexity of wild chimpanzee habitats.

**Recommendation EA4:** 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.

## **Animal Program Management Considerations**

Additional animal program elements that must be considered for appropriate captive chimpanzee management include enrichment programs, training programs, human interactions, and individualized care.

### Enrichment Programs

Enrichment programs for captive chimpanzees should be formulated to address the range of natural behaviors of this species and ensure appropriate psychological and cognitive stimulation. Wild chimpanzees spend the majority of their waking hours foraging for food, and they feed on hundreds of different fruits, foliage, roots, shoots, and stems as well as insects, birds, and small mammals. In addition to fulfilling nutritional needs, daily foraging provides opportunities for physical activity, environmental exploration, and cognitive engagement.

**Recommendation EA5:** 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.

A key element of chimpanzee ethology is the strong motivation to build new arboreal nests every night in which to sleep. Extant research has shown that chimpanzees benefit from complex substrates and provision of nesting materials (Chamove et al., 1982; Brent, 1992; Baker and Aureli, 1997).

**Recommendation EA6:** Chimpanzees must be provided with materials to construct new nests on a daily basis.

Chimpanzees are highly cognitively adept animals, and in the wild, they use this intelligence in a number of ways. Appropriately complex physical and social environments provide a wide range of cognitive challenges. However, elements that provide additional problem-solving opportunities, such as puzzles and tool-use tasks, are necessary to satisfy their inquisitive personalities. Allowing chimpanzees to make meaningful choices concerning all aspects of their daily lives is an important component of species-appropriate management. Meaningful choices can include selecting between types of foods, choosing whether to spend time indoors or outdoors, and determining the types of social groupings and activities in which to participate.

**Recommendation EA7:** The environmental enrichment program developed for chimpanzees must provide relevant opportunities for choice and self-determination.

## Animal Training Programs

The use of positive-reinforcement training to facilitate necessary veterinary treatment or aspects of research has measurable behavioral and physiological benefits (Laule et al., 2003; Lambeth et al., 2006; Laule and Whitaker, 2007; Perlman et al., 2010). The IOM committee recommended that chimpanzees engaged in research protocols be acquiescent. The Working Group defines “acquiescence” as voluntary participation in an activity based solely on positive reinforcement training and not involving forced participation or engagement by coercion. According to this definition, animals choose whether to participate or not based on their own volition.

**Recommendation EA8:** 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.

## Human Interactions

Interactions with caregivers, behaviorists, veterinarians, and scientists are an inevitable part of captive chimpanzee life. Ensuring that these relationships do not unnecessarily degrade a chimpanzee’s living conditions is essential. The Working Group has embraced the concept of a culture of care that should be promoted in ethologically appropriate environments. In a culture of care, chimpanzees are managed in a manner that engenders respect and mutually positive human–animal relationships. In some cases, this approach might not be the most convenient means of accomplishing an activity or task for the human involved. Environments in which caregivers or others represent negative or threatening stimuli have a negative impact on chimpanzees and are not ethologically appropriate.

**Recommendation EA9:** 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.

## Individualized Animal Care

It is widely accepted that chimpanzees are capable of exhibiting a wide range of emotions; expressing personality; and demonstrating individual needs, desires, and preferences. Although the Working Group’s recommendations regarding ethologically appropriate physical and social environments for chimpanzees are geared toward the majority of captive individuals, these environments must also meet individual physical and social needs.

An appropriate management environment is one that assesses, defines, and addresses individual chimpanzee needs and preferences in the context of providing opportunities for individuals to

meet their species-typical needs. In some cases, chimpanzees might have underlying physical infirmities or social or behavioral maladjustments that make them better suited to living in a smaller group than those recommended above. As long as such management decisions are due to exceptional individual needs rather than institutional, research, or management requirements or convenience, these strategies might be within the scope of ethologically appropriate physical and social environments. Individuals with exceptional social, psychological, behavioral, or physical needs probably do not represent ideal research subjects.

**Recommendation EA10:** 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.

### **Additional Considerations**

Although chimpanzees might require personalized environments in exceptional circumstances or due to individual needs, the aforementioned recommendations reflect ethologically appropriate physical and social environment conditions that apply to all NIH-owned and NIH-supported chimpanzees maintained in captivity for research purposes. This section makes clear the distinction between ethologically appropriate and ethologically inappropriate physical and social environments and discusses the application of ethologically appropriate conditions to temporary or transitional housing.

- A. Ethologically appropriate environments are those that meet the full range of physical, social, and management characteristics described above. Chimpanzee groups are large and complex, and they feature a core of multi-male leadership. Spaces are large enough to promote subgrouping, and chimpanzees have near-constant access to outdoor areas in which they can:
  - a. Range widely in an enclosure that permits some degree of subgroup partitioning from main groups, exploration, and territoriality;
  - b. Climb high, with numerous opportunities to travel, forage, and nest off the ground;
  - c. Use nesting materials that are provided daily;
  - d. Engage in diverse learning opportunities, including the ability to use complex naturalistic materials, substrates, and foliage, and opportunities to develop and use tools;
  - e. Make meaningful choices concerning their environment and living conditions;
  - f. Forage widely among varied sources; and
  - g. Form positive human–animal relationships within a management culture that embraces individualized care while minimizing adverse stress for chimpanzees in all aspects of their lives.

Ethologically appropriate physical and social environments should be available to house NIH-owned and NIH-supported research-active and research-inactive chimpanzees within 3 to 5 years.

- B. Ethologically inappropriate environments are those in which the aforementioned components of complexity and stimulation are not available. Environments that house smaller groups of animals and have only moderate complexity are not acceptable for long-term housing of chimpanzees. Similarly, environments in which chimpanzees are managed through the use of squeeze cages and frequent darting or tranquillization for holding or experimental purposes are not acceptable for long-term housing of chimpanzees.

Examples of ethologically inappropriate housing for long-term housing of chimpanzees include the provision of only standard indoor-outdoor run cages, outdoor geodesic housing structures, and primarily indoor environments. These housing systems, on their own, do not have the characteristics of ethologically appropriate environments and must not be used to house chimpanzees on a long-term basis.

- C. Temporary housing conditions that do not have all of the above characteristics of ethologically appropriate housing might be required for captive chimpanzees used for certain active research protocols. Temporary housing conditions might be necessary to conduct biomedical research that meets the IOM committee's criteria but requires short-term containment or periods of close observation or in other exceptional circumstances. Likewise, some medical treatments or behavioral management initiatives might require housing chimpanzees outside of ethologically appropriate environments for short periods of time. Examples of such events include preventive health examinations and related sedation as well as noninvasive and voluntary cognitive testing.

The Working Group defines “temporary housing conditions” as those needed to hold animals for between 24 hours and 21 days. Examples of temporary housing conditions include standard indoor-outdoor run cages, outdoor geodesic housing structures, and small outdoor corrals.

Chimpanzees should spend as little time as possible in these housing conditions and should continue to be socially housed. Efforts should be made to provide indoor-outdoor housing for the duration of a study. Prolonged housing in ethologically inappropriate environments (e.g., for months) should not be permitted, especially if the main justification is human convenience or cost.

- D. Transitional housing conditions that do not have all of the above characteristics of ethologically appropriate environments might be required for the next 3 to 5 years to accommodate current NIH-owned and NIH-supported research-active and research-inactive chimpanzees until ethologically appropriate primary living spaces become available. Transitional housing conditions might include outdoor corrals or outdoor geodesic housing structures.

Transitional housing conditions are by definition an interim solution. These conditions alone are not intended for long-term housing of chimpanzees under any circumstance and should only be approved after detailed plans for achieving ethologically appropriate physical and social environment conditions have been formalized.

When chimpanzees are housed in transitional housing conditions, every attempt should be made to provide the animals with daily access to the outdoors and to improve their primary living spaces and animal program management. These transitional environments should comply with the recommendations provided in this report to the extent possible.

The IOM committee stipulated that all chimpanzees used in biomedical and in comparative genomics and behavioral research must be maintained in ethologically appropriate physical and social environments. Transitional housing therefore provides an interim solution for the approval of new grants and contracts, but only within a strict 5-year time limit.

## Section 4. Review of Currently Active NIH-Supported Research Using

The Working Group used its definition of “ethologically appropriate physical and social environments,” described in the previous section, to help fulfill its charge of determining whether currently active NIH-supported research projects using chimpanzees comply with the IOM principles and criteria. This section describes the process the Working Group used to evaluate currently active projects and summarizes the recommendations regarding continuing or ending the projects that the Working Group delivered to the Council of Councils.

The Working Group was also tasked with providing advice on the process for closing any studies that do not comply with the IOM principles and criteria. For any studies that the Working Group recommended to “end,” the NIH is in the best position to work with the scientist, resource director at the facility that maintains the chimpanzees in question, and other relevant parties to ensure that the scientific value of the research is preserved.

The Working Group reviewed 30 projects that involve the use of NIH-owned or NIH-supported chimpanzees. For each project, the Working Group determined whether to continue the study, end the study, or conditionally approve the study to continue. The guidance for these recommendations is as follows:

- Continue: 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.
- End: 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.
- Conditionally approved to continue: One of the IOM principles is that the chimpanzees must be housed in an “ethologically appropriate” environment. At the time that the Working Group reviewed the active NIH projects, the group had not formally identified the characteristics of ethologically appropriate environments. Working Group members therefore recommended that projects that met all of the other IOM principles and criteria be “conditionally approved to continue.” “Conditionally approved to continue” 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. Continued maintenance, husbandry, welfare, and veterinary care of chimpanzees are at the discretion of the NIH as and until suitable, ethologically appropriate environments become available. Finally, if the principal investigator elects to submit a competitive renewal application for the project, that application will be reviewed under the guidance—including the definition of “ethologically appropriate environments”—that the NIH establishes for the use of

chimpanzees in research. The Working Group made provisions for interim housing for chimpanzees (see Section 3 above) so that new grants and contracts can be approved, but with a strict cap of 5 years.

The Working Group classified most of the 30 projects that it reviewed into one (or both) of the two categories suggested in the IOM report—(1) biomedical research and (2) comparative genomics and behavioral research—and determined whether each of these projects complied with the IOM criteria for that category of research. For projects that fit neither category, the Working Group determined whether the research complied with the IOM guiding principles.

*Biomedical Research:* The Working Group reviewed 9 biomedical research projects on immunology, bioterrorism, infectious agents, or hepatitis. The Working Group recommended conditional approval to continue for 3 projects involving immunology and infectious agents (e.g., hepatitis) and that the NIH end the other 6 projects.

*Comparative Genomics and Behavioral Research:* The Working Group reviewed 13 comparative genomics or behavioral research projects. The behavioral projects addressed cognition, perception, communication, development, motor control, altruism, memory, or brain structure and function. The Working Group recommended continuing or conditionally approving to continue 8 projects. Six of these projects involved behavioral research on some combination of chimpanzee cognition, perception, memory, learning, altruism, development, or brain structure and function. Two of the projects were comparative genomics/proteomics studies. The Working Group recommended ending the remaining 5 projects.

*Colony Housing and Care Projects:* The Working Group reviewed 8 projects involving chimpanzee colony housing, care, and maintenance or related support services. The Working Group classified these projects as biomedical research or behavioral or comparative genomics research if the project focused on supporting research (i.e., performed procedures required by a research protocol). The Working Group recommended conditional approval to continue for 7 of these projects, including all necessary veterinary care for the health of these chimpanzees, and recommended ending procedures to support research in 3 of these 7 projects. The Working Group recommended ending 1 project involving chimpanzee colony housing, care, and maintenance.

### **Working Group Recommendations on Currently Active Projects**

The Working Group presented its recommendations on the 30 projects it had reviewed to the Council of Councils during closed-session meetings on September 5, 2012,<sup>9</sup> October 29, 2012,<sup>10</sup> and January 8, 2013. The Council of Councils accepted all of the Working Group's recommendations. Table 3 summarizes the Working Group's recommendations.

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<sup>9</sup> September 5, 2012, meeting: <http://www.gpo.gov/fdsys/pkg/FR-2012-08-10/html/2012-19712.htm>

<sup>10</sup> October 29, 2012, meeting: <http://www.gpo.gov/fdsys/pkg/FR-2012-10-03/pdf/2012-24270.pdf>

**Table 3: Working Group Recommendations to the NIH Council of Councils Concerning Continuation of Current NIH-Funded Research Involving Chimpanzees**

		Working Group Recommendations			Recommendations
		Continue	Conditionally Approved to Continue	End	
Biomedical research	9	0	3*	7*	<ul style="list-style-type: none"> <li>• Conditionally approved to continue for 3 projects involving immunology and infectious agents</li> <li>• End 6 projects</li> </ul>
Comparative genomics and behavioral research	13	2**	7**	5	<ul style="list-style-type: none"> <li>• Continue or conditionally approved to continue for 6 behavioral research and 2 comparative genomics/proteomics studies</li> <li>• End 5 projects</li> </ul>
Colony housing and care	8	0	7 <sup>†</sup>	4 <sup>†</sup>	<ul style="list-style-type: none"> <li>• Conditionally approved to continue for 7 projects</li> <li>• End 1 project and the research component of 3 conditionally approved projects</li> </ul>

\*The Working Group recommended conditionally approving part of 1 biomedical research project and ending the other portion of the project. This project is included in the totals in both the “Conditionally Approved to Continue” and “End” columns.

\*\*The Working Group recommended continuing part of 1 comparative genomics and behavioral research project and conditionally approving another part of that project. This project is included in the totals in both the “Continue” and “Conditionally Approved to Continue” columns.

<sup>†</sup>The Working Group recommended conditionally approving to continue parts of 3 colony housing and care projects and ending the research portions of these projects. These projects are included in the totals in both the “Conditionally Approved to Continue” and “End” columns.

## **Section 5. Size and Placement of Research-Active and Research-Inactive Populations of NIH-owned and NIH-supported Chimpanzees**

This section provides an overview of chimpanzees owned or supported by the NIH and the Working Group's assessment of the future need to use chimpanzees in NIH-supported research (including research on new, emerging, and reemerging diseases). This section also offers recommendations regarding the size and placement of chimpanzees required for future research supported by the NIH. The Working Group members based their recommendations regarding the size of the chimpanzee population needed for research in part on currently active NIH-supported projects (described in Section 4 of this report). The Working Group members also considered the advice they received from content experts and current research facility administrators to develop their recommendations on population size.

### **Background**

As of October 23, 2012, NIH owns and supports the care and maintenance of 670 chimpanzees, of which 451 are currently designated as either research active or research inactive. These chimpanzees live at the Michale E. Keeling Center for Comparative Medicine and Research (Bastrop, Texas), Southwest National Primate Research Center (San Antonio, Texas), and the Alamogordo Primate Center (Alamogordo, New Mexico). An additional 109 NIH-owned chimpanzees have been designated as retired and are living in the federal sanctuary system facility at Chimp Haven (Keithville, Louisiana). Another 110 chimpanzees residing at the New Iberia Research Center (New Iberia, Louisiana) were designated as ineligible for biomedical research on September 21, 2012<sup>11</sup>, and will be moved to the federal sanctuary. Finally, NIH supports research projects using 91 chimpanzees living at the Southwest National Primate Research Center (San Antonio, Texas) that the NIH does not own. This information is summarized in Table 4.

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<sup>11</sup> NIH plans to relocate its chimpanzees from New Iberia to the Federal Sanctuary System: <http://www.nih.gov/news/health/dec2012/od-18.htm>

**Table 4. Census of NIH-Owned and NIH-Supported Chimpanzees, as of October 23, 2012<sup>12</sup>**

	<b>NIH-Owned and Supported</b>	<b>NIH- Supported but Not Owned</b>	<b>Total</b>
<b>Research Chimpanzees at Research Facilities</b> (research-active and research-inactive chimpanzees)			
Michale E. Keeling Center for Comparative Medicine and Research, The University of Texas M.D. Anderson Cancer Center, Bastrop, TX	167	0	167
*Southwest National Primate Research Center, Texas Biomedical Research Institute, San Antonio, TX	24	91*	115
<b>Total at Research Facilities</b>	<b>191</b>	<b>91</b>	<b>282</b>
<b>Research Chimpanzees at Research Reserve Facility</b> (research inactive)			
Alamogordo Primate Facility, Alamogordo, NM	169	0	169
<b>Total Research Chimpanzees</b>	<b>360</b>	<b>91</b>	<b>451</b>
<b>Retired Chimpanzees</b>			
Chimp Haven, Inc., Keithville, LA	109**	0	109
New Iberia Research Center, The University of Louisiana at Lafayette, New Iberia, LA	110***	0	110
<b>Total Research and Retired Chimpanzees</b>	<b>579</b>	<b>91</b>	<b>670</b>

\*Owned by Southwest National Primate Research Center and supported with funds from the NIH

\*\*Chimpanzees retired under the CHIMP Act to the federal sanctuary system

\*\*\*Designated as permanently ineligible for biomedical research on September 21, 2012, and to be retired over the next 12-15 months: <http://www.nih.gov/news/health/dec2012/od-18.htm>

The Working Group was charged with determining the size and placement of NIH-supported chimpanzees in the context of the IOM principles and criteria (IOM, 2011). Two primary factors influence any consideration of the size and placement of these chimpanzees: (1) the estimated future need for this population and (2) the ability of current and planned environments to develop the characteristics of ethologically appropriate physical and social environments that are defined in Section 3 above.

### **Future Need for Chimpanzees in Research**

First, it is clear from the 2011 IOM report that in most current invasive research, the use of chimpanzees is not essential. In fact, the IOM committee specifically notes that only a narrow

<sup>12</sup> Costs for Maintaining Humane Care and Welfare of Chimpanzees, October 23, 2012: [http://dpcpsi.nih.gov/orip/cm/chimpanzee\\_maintenance.aspx](http://dpcpsi.nih.gov/orip/cm/chimpanzee_maintenance.aspx)

range of studies meets its criteria for biomedical research relevance and continuation. From the IOM report:

*Most current use of chimpanzees for biomedical research is unnecessary...* (pp. 66–67)

*The present trajectory indicates a decreasing scientific need for chimpanzee studies due to the emergence of non-chimpanzee models and technologies.* (p. 67)

The IOM committee identified only two areas of invasive research in which the use of chimpanzees might be valuable: continued development of monoclonal antibodies and development of a prophylactic hepatitis C virus vaccine (although the IOM committee did not reach consensus on the latter). The IOM committee also left open the possibility that research on new, emerging, or reemerging diseases might require the use of chimpanzees.

#### Predictions of Future Need Based on the Use of Chimpanzees in Current 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. Details on this process and the Working Group's recommendations are provided in Section 4 of this report. 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. Assessments of the size of future research chimpanzee populations must reflect this fact. Furthermore, it appears to be likely that over time, the amount of invasive biomedical research on chimpanzees will diminish to such an extent that all research-active and research-inactive chimpanzees could be retired.

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. This research includes passive behavioral studies (that do not require any intervention with the chimpanzee group) and investigations of chimpanzee cognition, chimpanzee health, and genomics. Although unable to quantify the future demand for noninvasive research on chimpanzees, the Working Group was able to conditionally approve to continue several projects involving comparative genomics or behavioral research involving 290 chimpanzees. The Working Group agreed that the need to use chimpanzees in this type of research is not negligible and opportunities for such research should be made available to the scientific community. Nonetheless, the Working Group concluded that maintaining a large reserve colony of chimpanzees for minimally invasive research is not necessarily justified because many of these NIH research needs could be met in nontraditional research settings, such as accredited sanctuaries and zoos, as long as such settings provide ethologically appropriate physical and

social environments. The Working Group thus recommended that the NIH re-examine programmatic priorities in these areas of research.

### Predictions of Future Need Based on the Assessments of the Emerging Diseases Subgroup

The Working Group engaged a panel of experts in infectious diseases and laboratory biosafety (Emerging Diseases Subgroup) to provide advice on the number of chimpanzees, if any, needed to address new, emerging, and reemerging diseases or unanticipated threats to human health. The full report of the Emerging Diseases Subgroup is in Appendix G.

The IOM committee highlighted the many human health benefits gained from previous and currently ongoing biomedical research using chimpanzees (IOM, 2011). The committee acknowledged the difficulties of predicting or forecasting the future need for the chimpanzee as an animal model and human surrogate. Nevertheless, due in part to the emergence of non-chimpanzee models and technologies, the committee determined that the need for chimpanzee studies would decrease, but likely not be entirely eliminated, in the future. Specifically, the committee recognized that “...a new, emerging, or reemerging disease or disorder may present challenges to treatment, prevention, and/or control that defy non-chimpanzee models and technologies and therefore may require the future use of the chimpanzee” (IOM, 2011, p. 67).

In its deliberations, the Emerging Diseases Subgroup affirmed the findings of the IOM committee regarding the future use of chimpanzees in biomedical research on infectious diseases, namely that the NIH should limit the use of chimpanzees in biomedical research to studies that comply with the IOM principles and criteria. In addition, the subgroup made the following observations about issues not addressed by the IOM committee report:

- As of January 22, 2013, approximately 75 percent of emerging infectious diseases are of zoonotic origin, and about 25 percent of these diseases derive from nonhuman primate host species (Woolhouse and Gowtage-Sequeria, 2005; Jones et al., 2008).
- Scientific evidence has demonstrated that infectious diseases can be transmitted from chimpanzees to humans and vice versa (Jones et al., 2008; Köndgen et al., 2008; Schaumburg et al., 2012).
- Historical scientific evidence indicates that chimpanzees could be an animal reservoir and zoonotic source of a new, emerging, or reemerging human infectious disease.
- How often an “emergent” event will take place and whether a response to such an event would involve the use of chimpanzees is impossible to predict.
- The number, ages, and sexes of chimpanzees required for a definitive infectious disease study would depend on many parameters, including the purpose of the model’s use.
- Infectious disease research in chimpanzees would probably not be considered unless an episode of direct transmission from chimpanzees to humans was clearly demonstrated or a response to an “unknown unknown” (a novel emerging disease and/or bioterrorism agent for which all other approaches to develop prevention and control strategies have failed) required the use of chimpanzees.
- Infectious disease research would warrant the use of chimpanzees only in unique and rare situations (e.g., a new, emerging disease of exceptional lethality that threatens the public health).

- 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).
- Even for highly virulent Ebola and monkeypox viruses, significant research and human health advances (e.g., drug development and vaccines) have been achieved using smaller animal models.
- To the Working Group’s knowledge, all infectious disease research studies conducted on chimpanzees in the last 20 years have been survival experiments involving nearly exclusively animal biosafety level 2 (ABSL2) infectious agents (e.g., hepatitis B, hepatitis C, and HIV).
- To the Working Group’s knowledge, the NIH has never supported any research employing chimpanzees under higher biocontainment-level (i.e., ABSL3 or ABSL4) conditions.
- In some very rare cases of research on infectious diseases that present an exceptional threat to public health (e.g., an “unknown unknown”), the theoretical possibility of needing to use chimpanzees in the highest biocontainment-level (i.e., ABSL 4) facilities exists. However, none of the ABSL4 facilities in the United States is designed to accommodate research on chimpanzees, and substantial planning, time, and financial resources would be necessary to create such capability.
- Current federal regulatory guidelines prohibit the return of animals used in ABSL3 or ABSL4 studies to lower biocontainment-level conditions (e.g., to an ABSL2 facility or sanctuary) (Centers for Diseases Control and Prevention, 2009).
- 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.

### Ethologically Appropriate Physical and Social Environments

The ability of current or planned facilities to provide the conditions of ethologically appropriate physical and social environments is an additional factor to consider when determining the placement of NIH-owned and NIH-supported chimpanzees. “Ethologically appropriate physical and social environments” is a new and previously undefined term. For this reason, it is unlikely that all existing housing environments in current research facilities will provide all of the characteristics of ethologically appropriate environments that the Working Group recommends. Substantial financial resources will probably be needed to physically alter facilities to create fully ethologically appropriate environments. In addition, significant changes to animal program management will probably be needed.

### **Colony Size and Placement Recommendations**

Given the highly diminished need for chimpanzees as research subjects for invasive biomedical research, the Working Group proposes the following recommendations:

**Recommendation SP1:** 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 species-appropriate environment currently available and thus is the preferred environment for long-term housing of chimpanzees no longer required for research.

**Recommendation SP2:** 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.

**Recommendation SP3:** This small chimpanzee colony should be maintained at a facility that has the characteristics of ethologically appropriate physical and social environments described in this 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.

**Recommendation SP4:** 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.

**Recommendation SP5:** The NIH should review its funding priorities for comparative behavioral, cognitive, and genomics 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.

**Recommendation SP6:** 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.

**Recommendation SP7:** 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.

**Recommendation SP8:** 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.

**Recommendation SP9:** 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.

## **Section 6. Review Process for Future Proposals to Use Chimpanzees in NIH-Supported Research**

The final element of the Working Group's charge was to develop a review process for considering whether the potential future use of chimpanzees in NIH-supported research is scientifically necessary and consistent with the IOM principles and criteria. In developing this process, the Working Group considered the IOM guidance on this topic, its experience reviewing currently active NIH-supported research using chimpanzees, and its assessment of and recommendations regarding ethologically appropriate physical and social environments (described in Section 3 of this report).

This section summarizes the IOM committee's guidance regarding the review of research applications for NIH-funded research and a new NIH committee to review future requests to the NIH involving the use of chimpanzees for research. This section also includes recommendations regarding the composition and responsibilities of this committee as well as the process that the committee should use to review research applications.

### **IOM Guidance**

The IOM committee provided a policy rubric for assessing the need for chimpanzees in biomedical, comparative genomics, and behavioral research and recommended developing an independent committee to review applications for NIH-funded research using chimpanzees (IOM, 2011). From the IOM report:

*The committee believes that assessment of potential future use of the chimpanzee would be strengthened and the process made more credible by establishing an independent oversight committee that uses the recommended criteria and includes public representatives as well as individuals with scientific expertise, both in the use of chimpanzees and alternative models, in areas of research that have the potential for chimpanzee use. (p. 70)*

*The committee cannot predict or forecast future need of the chimpanzee animal model and encourages use of the criteria established in this report when assessing the potential necessity of chimpanzees for future research uses. (p. 66)*

*...the NIH should evaluate the necessity of the chimpanzee in all grant renewals and future research projects using the chimpanzee model based on the committee's criteria. (p. 69)*

### **Oversight Committee Composition**

Although the IOM committee recommended that the NIH evaluate the need to use chimpanzees in grant renewals and future research projects based on the committee's principles and criteria, the IOM committee was not asked to provide plans for implementing this guidance. The Working Group therefore provides recommendations regarding the composition of the Oversight Committee for Proposals Using Chimpanzees in NIH-supported Research (Oversight

Committee) and outlines a process for the Oversight Committee to use in reviewing applications to NIH for research involving chimpanzees.

**Recommendation RP1:** The NIH should replace the Interagency Animal Models Committee with an independent Oversight Committee for Proposals 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.

**Recommendation RP2:** 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.

**Recommendation RP3:** 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.

A majority vote based on the full committee membership will be necessary to determine whether a project complies with the IOM principles and criteria. The Oversight Committee should have an odd number of members and should have no fewer than nine experts in at least the following key areas.

1. The Oversight Committee should include at least one scientific domain expert from each of the following categories:
  - a. Expert in infectious disease (e.g., virology or immunology);
  - b. Neuroscientist with expertise in cognitive and behavioral research in humans or nonhuman primates to determine a project's likelihood of providing otherwise-unattainable insights into behavior, mental health, emotion, or cognition; and
  - c. Geneticist or evolutionary biologist with expertise in comparative genomics, genetics, and/or evolution.

In some cases, at least one additional scientific domain expert will be needed on an ad hoc basis to assess and determine the necessity of using chimpanzees in the proposed research if the committee's standing members lack such expertise. The expert(s) should also have sufficient content knowledge to assess whether alternative models to the chimpanzee are available. Based on the current research using chimpanzees, ad hoc members might include, for example, virologists with expertise in hepatitis C virus as well as experts in transgenic animal models and in vitro systems.

2. Licensed, graduate veterinarian(s) with demonstrated expertise in the clinical care of nonhuman primates, preferably chimpanzees, should assess the health, care, and welfare of chimpanzees to be used in the proposed research and assess and determine the potential short-term and long-term health risks of the proposed studies<sup>13</sup> for the chimpanzees.
3. Primatologist(s) or individual(s) with similar demonstrated expertise in primate, and preferably chimpanzee, behavior should assess and determine the short-term and long-term impact of the proposed research plan on the behavioral needs of chimpanzees. These experts should also assess the quality of the interactions between the chimpanzees and the facility's research and care staff described in the proposals. In particular, these experts should determine the extent of positive reinforcement training that the chimpanzees have received (and continue to receive) to voluntarily participate in aspects of the research project so as to ensure chimpanzee acquiescence.
4. A bioethicist or individual(s) with bioethics expertise and experience as an institutional review board (IRB) member should assess whether the proposed research could be conducted ethically in humans instead of chimpanzees. Such assessments would not require the investigators to develop a comparable protocol for their research in humans or to obtain IRB approval of their proposal for chimpanzee research.
5. Statistician(s) should assess and determine the validity of the statistical analysis and interpretations used to calculate the numbers and use of chimpanzees in the proposed research.
6. At least two persons representing community interests and concerns who have not been directly involved in animal use for research, teaching, or testing but are able (or competent) to apply the IOM criteria to assess the necessity of using chimpanzees in the proposed research.
7. Non-voting NIH official(s) *ex officio* should advise on process issues and provide documents and/or relevant information as needed.

## **Review Process**

### Distinction Between Biomedical, Comparative Genomics, and Behavioral Research

The Working Group found that the distinction in the IOM report between biomedical research and comparative genomics and behavioral research is challenging to implement in reviewing applications. For example, this distinction imposes a potential dichotomy between mental functioning and the functioning of components outside the central nervous system, and this

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<sup>13</sup>A determination by the Oversight Committee that a study could be conducted in human subjects does not imply that the NIH has approved the proposal's plan for protecting human subjects. Investigators who choose to propose human studies in place of chimpanzee studies need to revise and resubmit their proposal, including documentation of applicable institutional review board approval.

dichotomy is not warranted based on current scientific understanding. More specifically, because many mental disorders affect the brain, research on comparative cognition (such as the origins of language or social behavior that are related to a variety of neuropsychiatric or developmental conditions) can and should be construed as basic biomedical research. The same is true of research in evolution and comparative genomics. Furthermore, implementation based on this dichotomy would require that less invasive, and potentially less harmful, behavioral research on chimpanzees meet the standard of acquiescence (first mentioned on p. 6 of the IOM's 2011 report and defined by the Working Group in the glossary in this report) that in the current IOM rubric would not be applied to biomedical research, even though most biomedical research is more invasive.

The Working Group suggests avoiding the distinction between biomedical and behavioral and comparative genomics research and that all research on chimpanzees follow the same decision-making algorithm process, as guided by the IOM principles and criteria. The basic process in all cases involves an initial scientific assessment that includes a determination that:

- The knowledge gained is necessary to advance the public's health or will lead to otherwise unattainable insight into comparative genomics, normal and abnormal behavior, mental health, emotion, or cognition;
- There is no other suitable animal model available, such as in vitro, nonhuman in vivo, or other models, by which the knowledge could be obtained; and
- The research in question cannot be performed ethically on human subjects.

#### Process to Apply for Research Using Chimpanzees

**Recommendation RP4:** 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.

**Recommendation RP5:** 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.

**Recommendation RP6:** 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/or 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.

### Review Considerations

If the proposed research passes the initial scientific assessment, the Oversight Committee will determine whether the research can be conducted in ethologically appropriate environments (see Section 4 of this report for a discussion of ethologically appropriate physical and social environments).

The IOM committee recommended assessing whether “*the benefits gained from research on animals are sufficient to outweigh the harms caused in the process*” to determine whether the use of chimpanzees in research is justified (IOM, 2011, p. 15). To guide the process of balancing human health interests and chimpanzee well-being, the Working Group offers several major considerations. The purpose of the research is to achieve a specific benefit—an improvement in human health. Thus, determining what the research is designed to learn and the likelihood that this information will lead to an improvement in human health is important. However, making such a determination is particularly challenging for basic science research, such as genomic, evolutionary, or cognitive research, whose aim is to produce general knowledge of as yet largely unpredictable value to public health. For this reason, determinations of the benefits of basic research should be based on whether the research will lead to otherwise unattainable insight.

The severity and duration of potential physical or psychological harm (in the form of discomfort, deterioration in social status, or injury) to chimpanzees and the probability that the harm will occur must be assessed. For the review process that the Oversight Committee will use, the Working Group defined this concept as the “burden” on the chimpanzees. Invasive interventions typically impose higher burdens than noninvasive ones, and biomedical research might impose a significant burden more frequently than behavioral and genomic studies. However, the Working Group found that these research categories are all imperfect proxies for the real concern, which is the actual burden on the chimpanzees.

If an experiment has benefits that greatly outweigh its burdens, it might be approvable but not until the protocol has been examined to determine whether the benefit-to-burden ratio can be further improved by, for example, making additional efforts to keep the chimpanzees comfortable or to shorten the duration of the intervention. The benefits should be reasonably maximized and burdens reasonably minimized.

### Decision-Making Algorithm

1. Does this research use chimpanzees?
  - a. If no, end of survey.
  - b. If yes, continue to Q2.

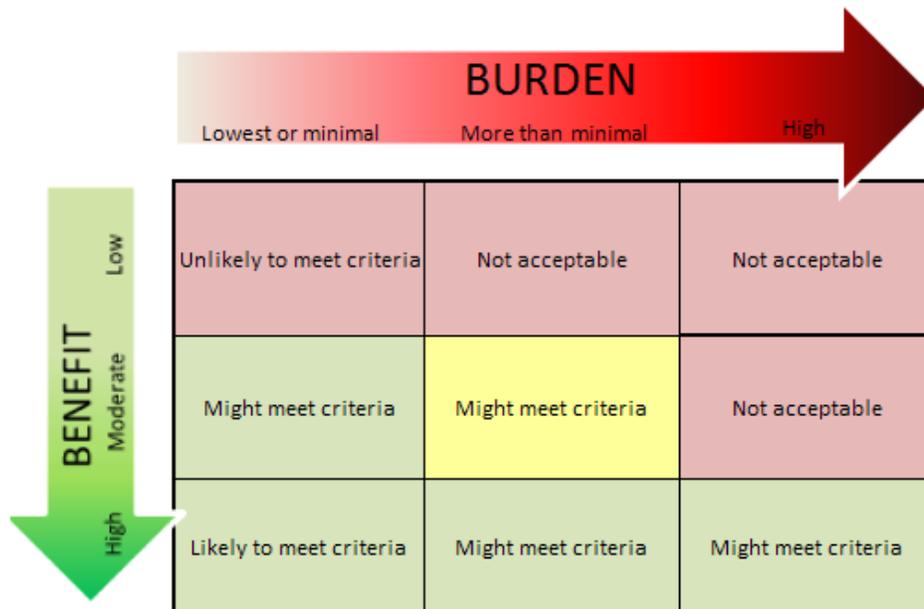
2. Does this research use only previously collected biospecimens, including blood, tissue, or any materials collected postmortem? Does the research solely involve the observation of animals in their native, natural habitat? Is the research limited to noninvasive sample collections (e.g., of fecal, urine, or sperm plug specimens) in a manner that does not result in contact or otherwise interfere with the chimpanzees during the sample collection process?
  - a. If the answer to any of these questions is yes, end of survey. This work is not under the purview of the Oversight Committee.
  - b. If the answer to all of the questions is no, continue to Q3.
3. Is the purpose of this research primarily to improve the health and well-being of chimpanzees?
  - a. If yes, the investigator must provide an explanation that will be reviewed by the committee. In this explanation, the investigator must demonstrate that the chimpanzee's use is in the best interest of the chimpanzee and addresses the mission of the NIH. Such an explanation is not necessary for standard-of-care or compassionate use of treatments.
  - b. If no, continue to Q3c.
  - c. Is the purpose of this research for the benefit of humans?
    - i. If yes, proceed to Q4.
    - ii. If the purpose of this research is not for the benefit of humans or chimpanzees, chimpanzee research is not permitted.
4. Are other suitable models, such as in vitro, nonhuman in vivo, or other models, available for the research in question?
  - a. If yes, chimpanzee research is not permitted.
  - b. If no, proceed to Q5.
5. Can the research in question be performed ethically<sup>14</sup> on human subjects with the prospect of achieving comparable results?
  - a. If yes, chimpanzee research is not permitted.
  - b. If no, proceed to Q6.
6. Will forgoing the use of chimpanzees for the research in question significantly slow or prevent important advancements in genomics; evolutionary theory; human behavioral, cognition, or emotions research; or important advances in the prevention or treatment of life-threatening or debilitating human conditions?

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<sup>14</sup> One characteristic that the Working Group suggests using to answer this question is whether the research on humans would be potentially approvable by an institutional review board.

- a. If no, chimpanzee research is not permitted.
  - b. If yes, proceed to Q7.
7. Will physical, psychological, and emotional burdens on the chimpanzees be limited by minimizing the number of chimpanzees used, the duration of the experiment, and the discomfort of the procedures and by performing the work on acquiescent chimpanzees that have been trained to present for blood draws or anesthesia or to participate in the research and can do so voluntarily?<sup>15</sup>
- a. If no, chimpanzee research is not permitted.
  - b. If yes, proceed to Q8.
8. Are the remaining physical, psychological, and emotional burdens on the chimpanzees outweighed by the possible benefits to humankind and to science?
- a. If no, chimpanzee research is not permitted.
  - b. If yes, proceed to Q9.

The matrix below (Figure 1) provides a framework for balancing burdens on chimpanzees and potential benefits of research.



**Figure 1. Burden-Benefit Matrix**

<sup>15</sup> Evidence of voluntary participation is that each chimpanzee has the opportunity to choose not to participate at any given time.

The Working Group defined “*lowest or minimal burden*” studies as noninvasive or observational studies that cause little or no discomfort or stress in chimpanzees. Such studies might involve acquiescent participation in a study on cognition following positive reinforcement training or simple observation of behavior. Research involving only samples that are routinely obtained (e.g., leftover blood or urine) while an animal is under anesthesia for routine veterinary examinations also fall into this category.

“*More than minimal burden*” studies involve more potential risk or invasiveness, as reflected by the extent of pain, distress, fear, discomfort, or injury. Examples include studies involving voluntary separation of chimpanzees from their social group for a short time; any procedure that requires general anesthesia; any procedure that prolongs routine anesthesia during routine veterinary examinations; and intravenous injections or repeated blood sampling in non-anesthetized, acquiescent animals. Such research does not impose a high burden or risk, but it imposes more than the lowest level of burden.

“*High burden*” studies include most biomedical research involving measurable distress or physical alteration. Examples include those that result in the prolonged separation of chimpanzees from their social group (ethologically inappropriate environments as defined in Section 3 of this report); inoculation with an infectious agent; exposure to pharmaceutical agents or chemicals; food or water deprivation; or surgical procedures such as biopsies, laparoscopy, or prolonged physical restraint.

Using the burden-benefit matrix, investigators could easily show that studies in the bottom left box meet the IOM criteria because these involve a *lowest or minimal burden* and a *high benefit*. Protocols in the bottom row of boxes might meet the criteria because they have the potential to offer *high benefit* (colored in green, “likely to meet criteria” or “might meet criteria”), but as the burden increases, these studies will only be permissible if their clear human health benefits also increase. Hence, basic cognition, evolution, or genomic studies involving a high burden would not be allowable because although their scientific benefit might be high, this benefit does not outweigh the degree of burden on the animal (colored in red, “not acceptable”). Experiments with the *lowest or minimal burden* and *low benefit* also would not likely meet the criteria because they are not scientifically justified (colored in red, “unlikely to meet criteria”). Studies with *more than minimal burden* but *moderate benefit* could be acceptable because the perceived benefit might depend partially on their outcomes, which cannot be predicted a priori (colored in yellow, “might meet criteria”). Examples of current studies that might fall into this latter category are certain cognitive or comparative evolution studies involving neuroimaging.

9. Will the animals used in the proposed research be maintained in either ethologically appropriate physical and social environments or transitional housing (based on the characteristics discussed in Section 3 above) or in natural habitats?
  - a. If no, chimpanzee research is not permitted.
  - b. If yes, the IOM criteria for the use of chimpanzees in NIH-funded research have been met.

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 (see below).

### **Placement of Oversight Committee Review**

Information pertaining to a research proposal's review is kept confidential until the NIH Director or the director of the relevant NIH Institute or Center makes the final award decision. Doing so protects privileged information. The Working Group therefore offers the following recommendations.

**Recommendation RP7:** The Oversight Committee review should take place after the Center or Institute director approves a proposal so that the 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.

**Recommendation RP8:** 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).

**Recommendation RP9:** The Oversight Committee will determine whether each application meets or does not meet the IOM principles and criteria based on the 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.

## Section 7: Conclusion

This report by the Working Group on the Use of Chimpanzees in NIH-Supported Research provides 28 recommendations to the Council of Councils, a federal advisory committee of the NIH. The report completes the task of the Working Group, which was to advise the NIH on implementing the recommendations of the IOM report, *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* (IOM, 2011), by addressing the following four-point charge:

- 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.

In developing its recommendations, the Working Group solicited and reviewed public comments, considered the scientific use of chimpanzees in the 30 currently funded projects that involve chimpanzees, obtained advice from 11 external experts, and conducted field trips to 7 facilities that care for and house chimpanzees. These experiences gave the Working Group an informed view of three important perspectives: members of the public with considerable interest in this topic, scientists conducting research using chimpanzees, and facilities and staff that care for the chimpanzees on a daily basis.

The Working Group is pleased to have responded to each element of its charge and presents this report as its final deliverable. In submitting this report to the NIH Council of Councils on January 22, 2013, the Working Group concludes a series of activities thoughtfully conducted to facilitate NIH's implementation of the IOM recommendations.

## References

- Aureli F, de Waal F. Inhibition of social behavior in chimpanzees under high-density conditions. *Amer J Primatol.* 1997 Feb;41(3):213-228.
- Baker KC, Aureli F. Behavioural indicators of anxiety: an empirical test in chimpanzees. *Behav.* 1997;134(13/14):1031-1050.
- Baker KC, Ross SK. Outdoor access: the behavioral benefits to chimpanzees. *Amer J Primatol.* 1998;45(2):166.
- Bowen RA. The behavior of three hand-reared lowland gorillas, *Gorilla g. gorilla*, with emphasis on the response to a change in accommodation. *Dodo.* 1980;17:63-79.
- Brent L. Woodchip bedding as enrichment for captive chimpanzees in an outdoor enclosure. *Anim Welf.* 1992;1(3):161-170.
- Centers for Disease Control and Prevention. *Biosafety in Microbiological and Biomedical Laboratories.* 5<sup>th</sup> edition. HHS Publication No. (CDC) 21-111. Atlanta, GA: Centers for Disease Control and Prevention; 2009.
- Chamove AS, Anderson JR, Morgan-Jones SC, Jones SP. Deep woodchip litter: hygiene, feeding, and behavioral enhancement in eight primate species. *Int J Study Anim Prob.* 1982;3(4):308-318.
- Chapman CA, Wrangham RW, Chapman, LJ. Ecological constraints on group size: an analysis of spider monkeys and chimpanzee subgroups. *Behav Ecol Sociobiol.* 1995;36(1):59-70.
- Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science.* 1989 Apr 21;244(4902):359-362.
- Clark FE. Great ape cognition and captive care: can cognitive challenges enhance well-being? *Appl Anim Behav Sci.* 2011 Nov 30;135(1-2):1-12.
- Clarke AS, Juno CJ, Maple TL. Behavioral effects of a change in the physical environment: a pilot study of captive chimpanzees. *Zoo Biol.* 1982;1(4):371-380.
- Denton D, Weisinger R, Mundy NI, Wickings EJ, Dixson A, Moisson P, Pingard AM, Shade R, Carey D, Ardaillou R, Paillard F, Chapman J, Thiollet J, Michel J-B. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med.* 1995 Oct;1(10):1009-1016.
- Doran, DM. *Great Ape Societies.* Cambridge: Cambridge University Press; 1996.
- Dunbar RIM. The social brain hypothesis. *Brain.* 1998;9:10.

Goff C, Howell SM, Fritz J, Nankivell B. Space use and proximity of captive chimpanzees (*Pan troglodytes*) mother/offspring pairs. *Zoo Biol.* 1994;13(1):61-68.

Goodall J. *The Chimpanzee of Gombe: Patterns of Behavior*. Cambridge, MA: Harvard University Press; 1986.

Hopper LM, Lambeth SP, Schapiro SJ. An evaluation of the efficacy of video displays for use with chimpanzees (*Pan troglodytes*). *Amer J Primatol.* 2012 May;74(5):442-449.

Humphrey, NK. The social function of intellect. In: Bateson PPG, Hinde RA, eds. *Growing Points in Ethology*. Cambridge: Cambridge University Press; 1976: pp. 303-317.

Institute of Medicine. *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity*. Washington, DC: The National Academies Press; 2011.

Jones KE, Patel N, Levy M, Storeygard A, Balk D, Gittleman JL, et al. Global trends in emerging infectious diseases. *Nature.* 2008;451:990-993.

Köndgen S, Kühl H, N'Goran PK, Walsh PD, Schenk S, Ernst N, Biek R, Formenty P, Mätz-Rensing K, Schweiger B, Junglen S, Ellerbrok H, Nitsche A, Briese T, Lipkin WI, Pauli G, Boesch C, Leendertz FH. Pandemic human viruses cause decline of endangered great apes. *Curr Biol.* 2008 Feb 26;18(4):260-264.

Lambeth SP, Hau J, Perlman JE, Martino M, Schapiro SJ. Positive reinforcement training affects hematologic and serum chemistry values in captive chimpanzees (*Pan troglodytes*). *Amer J Primatol.* 2006 Mar;68(3):245-256.

Larsson M, Babcock E, Grakoui A, Shoukry N, Lauer G, Rice C, Walker C, Bhardwaj N. Lack of phenotypic and functional impairment in dendritic cells from chimpanzees chronically infected with hepatitis C virus. *J Virol.* 2004 Jun;78(12):6151-6161.

Laule G, Whittaker M. Enhancing nonhuman primate care and welfare through the use of positive reinforcement training. *J Appl Anim Welf Sci.* 2007;10(1):31-38.

Laule GE, Bloomsmith MA, Schapiro SJ. The use of positive reinforcement training techniques to enhance the care, management, and welfare of primates in the laboratory. *J Appl Anim Welf Sci.* 2003;6(3):163-173.

McGrew WC, Baldwin PJ, Tutin CE. Chimpanzees in a hot, dry and open habitat: Mt. Assirik, Senegal, West Africa. *J Human Evol.* 1981;10(3):227-244.

Mitani JC, Watts DP. Correlates of territorial boundary patrol behaviour in wild chimpanzees. *Anim Behav.* 2005 Nov;70(5):1079-1086.

*Nature.* 2011;474:252.

Newton-Fisher, NE. The home range of the Sonso community of chimpanzees from the Budongo Forest, Uganda. *African Journal of Ecology*. 2003 Jun;41(2):150-156.

Nishida T, Hiraiwa-Hasegawa M. Chimpanzee and bonobos: cooperative relationships among males. In: Smuts BB, Cheney DL, Seyfarth RM, Wrangham RW, Struhsaker TT, eds. *Primate Societies*. Chicago, IL: University of Chicago Press; 1987: pp. 165-177.

Perlman J, Horner V, Bloomsmith M, Lambeth SP, Schapiro SJ. *The Mind of the Chimpanzee: Ecological and Experimental Perspectives*. Chicago, IL: University of Chicago Press; 2010: pp. 320-331.

Pruetz JDE, McGrew WC. What does a chimpanzee need? Using natural behavior to guide the care and management of captive populations. In: Brent L, Wallis J, eds. *The Care and Management of Captive Chimpanzees*; San Antonio, TX: American Society of Primatologists; 2001: pp. 16-37.

Pusey A, Williams J, Goodall J. The influence of dominance rank on the reproductive success of female chimpanzees. *Science*. 1997 Aug 8;277(5327):828-831.

Ross SR, Calcutt S, Schapiro SJ, Hau J. Space use selectivity by chimpanzees and gorillas in an indoor-outdoor enclosure. *Amer J Primatol*. 2011 Feb;73(2):197-208.

Ross SR, Lukas KE. Use of space in a non-naturalistic environment by chimpanzees (*Pan troglodytes*) and lowland gorillas (*Gorilla gorilla gorilla*). *Appl Anim Behav Sci*. 2006 Jan;96(1/2):143-152.

Ross SR, Wagner, KE, Schapiro, SJ, Hau J. Differential ape behavior in two alternating environments: Comparing behavior in exhibit and short-term holding spaces. *Am J Primatol*. 2010;72:951-959.

Schaumburg F, Mugisha L, Peck B, Becker K, Gillespie TR, Peters G, Leendertz FH. Drug-resistant human *Staphylococcus aureus* in sanctuary apes pose a threat to endangered wild ape populations. *Am J Primatol*. 2012 Dec;74(12):1071-1075.

Traylor-Holzer K, Fritz P. Use of space by adult and juvenile groups of captive chimpanzees, *Pan troglodytes*. *Zoo Biol*. 1985;4:115-127.

Videan EN, Fritz J. Effects of short-and long-term changes in spatial density on the social behavior of captive chimpanzees (*Pan troglodytes*). *Appl Anim Behav Sci*. 2007;102(1):95-105.

Videan EN, Fritz J, Schwandt ML, Smith HF, Howell S. Controllability in environmental enrichment for captive chimpanzees (*Pan troglodytes*). *J Appl Anim Welf Sci*. 2005;8(2):117-130.

Woolhouse ME, Gowtage-Sequeria S. Host range and emerging and reemerging pathogens. *Emerg Infect Dis.* 2005;11(12):1842-1847.

Wrangham R. On the evolution of ape social systems. *Soc Sci Inform.* 1979;18(3):336-368.

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Members of the Working Group appreciate the opportunity to have been part of this important effort and hope that its efforts facilitate NIH's implementation of the IOM recommendations regarding the use of chimpanzees in research.

## **Appendix A: Working Group on the Use of Chimpanzees in NIH-Supported Research Membership Roster**

Daniel H. Geschwind, M.D., Ph.D. (co-chair), Gordon and Virginia Distinguished Professor of Neurology, Psychiatry and Human Genetics; Director, Center for Autism Research and Treatment, Semel Institute and Program in Neurogenetics, Department of Neurology, University of California, Los Angeles

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### **Members Who Participated in the Working Group for a Partial Term**

The following Working Group members did not complete their terms on the Working Group. They did not participate in writing or reviewing the draft report and, therefore, they have not expressed an opinion about the final report:

Stanley Lemon, M.D., Professor of Medicine, School of Medicine, University of North Carolina\*

Daniel J. Povinelli, Ph.D., Professor, Department of Biology; James S. McDonnell Centennial Fellow, University of Louisiana\*\*

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\*Dr. Lemon was a member of the Working Group between February and June 2012.

\*\*Dr. Povinelli was a member of the Working Group between February and September 2012.

\*\*\*Dr. Rice was a member of the Working Group between February and June 2012.

## **Appendix B: Biographies of Members of the Working Group on the Use of Chimpanzees in NIH-Supported Research**

**Daniel H. Geschwind, M.D., Ph.D.**, is the Gordon and Virginia MacDonald Distinguished Professor of Neurology and Psychiatry and Human Genetics at the University of California, Los Angeles (UCLA) School of Medicine. Dr. Geschwind obtained an A.B. in psychology and chemistry from Dartmouth College and an M.D./Ph.D. from Yale School of Medicine prior to completing his internship, residency, and postdoctoral fellowship at UCLA. He joined the UCLA faculty in 1997 and has published over 250 research papers in the field of neurogenetics. Dr. Geschwind's work integrates population genetics, functional genomics, and bioinformatics with basic and clinical neuroscience to understand neuropsychiatric disease pathogenesis and accelerate treatment development. In addition to his research, Dr. Geschwind is active on numerous scientific advisory and editorial boards and is a former member of the National Institute of Mental Health Scientific Advisory Council. He received the Derek Denny-Brown Neurological Scholar Award from the American Neurological Association in 2004 and the Scientific Service Award from Autism Speaks in 2008, and he is a member of the IOM.

**K.C. Kent Lloyd, D.V.M., Ph.D.**, is Associate Dean for Research and Graduate Education and Professor of Anatomy in the Department of Anatomy, Physiology and Cell Biology in the School of Veterinary Medicine at the University of California, Davis (UCD). Dr. Lloyd is a clinical veterinarian and research physiologist with expertise in targeted conditional mutagenesis of the laboratory mouse and physiology of the mammalian gastrointestinal tract, with special emphasis on mechanisms of enterogastric reflexes. As Director of the UCD Mouse Biology Program, Dr. Lloyd conducts research, teaching, and services using genetically altered mice. Dr. Lloyd is also an instructor in the veterinary and graduate curriculums, teaching renal and gastrointestinal physiology of monogastrics and ruminants to medical, veterinary, and graduate students and genetic manipulation of the mouse embryo to undergraduate and graduate students. Dr. Lloyd received his D.V.M. from UCD in 1983 and completed his Ph.D. in 1992 at UCLA. From 1993 to 1995, he was Assistant Professor of Medicine and Physiology at UCLA, and he was subsequently a visiting scientist at the European Molecular Biology Laboratory in Heidelberg, Germany, from 1994 to 1996. He has been at UCD since 1997.

**Alan D. Barrett, Ph.D.**, is Director of the Sealy Center for Vaccine Development, Professor of Pathology, and Professor of Microbiology and Immunology at the University of Texas Medical Branch. He obtained his B.S., M.S., and Ph.D. in arthropod-borne viruses (arbovirology) from the University of Warwick (1975–1983), followed by a postdoctoral fellowship at the London School of Hygiene and Tropical Medicine (1983–1985). Subsequently, he was Lecturer, Senior Lecturer, and Head of the Molecular Microbiology Research Group at the University of Surrey (1985–1993). Dr. Barrett is Chair of the Scientific Advisory Panel of the Singapore Environmental Health Institute and is a member of several national and international scientific advisory groups, including World Health Organization (WHO) advisory groups on dengue, encephalitis, and yellow fever vaccines; the Virus Diseases Panel of the Military Infectious Diseases Research Program; and the Scientific Organizing Committee of the Annual Global Vaccine Congress. He is an associate editor for *Vaccine* and has been the author or coauthor of more than 234 research papers, reviews, and book chapters.

**R. Alta Charo, J.D.**, is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin (UW) at Madison, where she is on the faculty of the Law School and the Medical School's Department of Medical History and Bioethics. She obtained an A.B. in biology from Harvard University in 1979 and a J.D. from Columbia University in 1982. Professor Charo also serves on the faculty of the UW Masters in Biotechnology Studies program and lectures in the M.P.H. program of the Department of Population Health Sciences. She has served on the UW Hospital clinical ethics committee and the university's Institutional Review Board and Bioethics Advisory Committee. Professor Charo serves on the expert advisory boards of several organizations focused on stem cell research, including the Juvenile Diabetes Research Foundation, WiCell, and the Wisconsin Stem Cell Research Program. In 1996–2001, Professor Charo was a member of President Clinton's National Bioethics Advisory Commission. Since 2001, she has been a member of the National Academy of Sciences (NAS) Board on Life Sciences, and she serves as liaison to or member of several NAS and IOM committees working in research ethics, public health ethics, and stem cell policy.

**Beatrice H. Hahn, M.D.**, is Professor of Medicine and Microbiology in the Division of Hematology/Oncology at the University of Pennsylvania Perelman School of Medicine. She is a microbiologist recognized for her work deciphering the primate origins of the human AIDS viruses HIV-1 and HIV-2 and the malaria parasite *Plasmodium falciparum*. She is known particularly for developing noninvasive methods to study the evolution, biology, natural history, and zoonotic potential of infectious agents in wild-living endangered primates, especially chimpanzees and gorillas. Dr. Hahn was born in Munich, Germany, and became a U.S. citizen in 2007. She received an M.D. from the University of Munich in 1981 and a doctorate in medicine in 1982, and she performed postdoctoral studies at the National Cancer Institute from 1982 to 1985. Hahn was a faculty member at the University of Alabama in Birmingham for 26 years, where she served as Co-Director of the Center for AIDS Research. In 2011, she joined the Departments of Medicine and Microbiology at the University of Pennsylvania. Dr. Hahn is a fellow of the American Academy of Microbiology, a member of the IOM, and a member of the National Academy of Sciences.

**Stephen Ross, Ph.D.**, is Director of the Lester E. Fisher Center for the Study and Conservation of Apes at Lincoln Park Zoo in Chicago. In this role, he directs a multidisciplinary team focused on advancing the knowledge of ape biology, improving the care and management of captive apes, and conserving and protecting wild ape populations. He holds a B.Sc. from the University of Guelph, an M.A. from the University of Chicago, and a Ph.D. from the University of Copenhagen. He has studied chimpanzee behavior for more than 17 years in a range of settings, including research centers, sanctuaries, and zoos. After joining Lincoln Park Zoo in 2000, Dr. Ross played a primary role in the design of the award-winning Regenstein Center for African Apes. In 2002, he was selected as Chair of the Chimpanzee Species Survival Plan<sup>®</sup>, a multi-institutional effort to manage the population of chimpanzees living in accredited zoos in North America. Dr. Ross founded Lincoln Park Zoo's Project ChimpCARE in 2009 to assess the housing and management of privately owned chimpanzees (pets and performers) to facilitate policy changes that will benefit this population.

**Patricia Turner, M.Sc., D.V.M., D.V.Sc.,** is Professor of Pathobiology and Program Leader of Graduate Studies in Laboratory Animal Science at the University of Guelph. She also manages the campus laboratory animal diagnostic pathology core and provides consultative laboratory animal pathology services. Her research interests include infectious diseases of laboratory animals, the influence of the environment on laboratory animal behavior and disease susceptibility, and anesthesia and analgesia of laboratory animals. Dr. Turner has a B.Sc. in biochemistry from McMaster University, an M.Sc. in pharmacology from Dalhousie University, a D.V.M. from Ontario Veterinary College, and a D.V.Sc. in comparative pathology from the University of Guelph. Following postdoctoral work at McGill University, Dr. Turner was Director of Animal Care Services and Assistant Professor of Pathology at Queen's University. She was subsequently a toxicology team representative in preclinical safety testing at Warner-Lambert and Pfizer. Dr. Turner is a Diplomate of the American College of Laboratory Animal Medicine and the American Board of Toxicology. In 2007, she was the inaugural recipient of the North American Animal Welfare Award, cosponsored by Procter & Gamble and the Humane Society of the United States. She is President of the Association of Primate Veterinarians.

#### **Biographies of Members Who Participated in the Working Group for a Partial Term**

**Stanley Lemon, M.D.,** is Professor of Medicine at the University of North Carolina. He received his undergraduate degree in biochemical sciences from Princeton University and his M.D. with honors from the University of Rochester. He completed postgraduate training in internal medicine and infectious diseases at the University of North Carolina at Chapel Hill and is board certified in both internal medicine and infectious diseases. From 1977 to 1983, he directed the Hepatitis Laboratory at the Walter Reed Army Institute of Research. Dr. Lemon joined the faculty of the University of North Carolina School of Medicine in 1983, serving first as Chief of the Division of Infectious Diseases and then Vice Chair for Research in the Department of Medicine. In 1997, Dr. Lemon moved to the University of Texas Medical Branch as Professor and Chair of the Department of Microbiology and Immunology. He served as permanent Dean of Medicine from 2000 to 2004. Dr. Lemon's personal research interests relate to the molecular virology and pathogenesis of the positive-stranded RNA virus responsible for hepatitis C.

**Daniel Povinelli, Ph.D.,** is Professor of Biology at the University of Louisiana in Lafayette. He received his undergraduate degree from the University of Massachusetts at Amherst and his doctorate from Yale University. He joined the faculty of the University of Louisiana in 1991. He was awarded a \$1 million James S. McDonnell Centennial Fellowship in 1999 and named one of "20 Scientists to Watch in the Next 20 Years" by *Discover* magazine in 2000. Dr. Povinelli's primary interests are in characterizing the evolution of higher-order cognitive functions in the great ape/human clade (humans, chimpanzees, gorillas, orangutans).

**Charles Rice, Ph.D.**, is the Maurice R. and Corinne P. Greenberg Professor in Virology at The Rockefeller University. Dr. Rice received his Ph.D. in biochemistry in 1981 from the California Institute of Technology, where he was subsequently a postdoctoral research fellow from 1981 to 1985. Before he joined The Rockefeller University in 2000, Dr. Rice spent 14 years on the faculty of the Washington University School of Medicine. Dr. Rice is Executive and Scientific Director of the Center for the Study of Hepatitis C, an interdisciplinary center established jointly by The Rockefeller University, New York-Presbyterian Hospital, and Weill Cornell Medical College. Dr. Rice is a member of the National Academy of Sciences.

## **Appendix C: Consultants to the Working Group on the Use of Chimpanzees in NIH-Supported Research**

Bruce M. Altevogt, Ph.D., Senior Program Officer, Institute of Medicine

Jeffrey P. Kahn, Ph.D., M.P.H., Robert Henry Levi and Ryda Hecht Levi Professor of Bioethics and Public Policy and Deputy Director for Policy and Administration, Berman Institute of Bioethics, Johns Hopkins University

Jay R. Kaplan, Ph.D., Professor of Pathology (Comparative Medicine) and Anthropology, Wake Forest School of Medicine; Director, Wake Forest University Primate Center

Stanley Lemon, M.D., Professor of Medicine, School of Medicine, University of North Carolina at Chapel Hill

Charles Rice, Ph.D., Maurice R. and Corinne P. Greenberg Professor in Virology, The Rockefeller University

Robert Sapolsky, Ph.D., John A. and Cynthia Fry Gunn Professor of Biological Sciences, Neurology and Neurological Sciences, Stanford University

## **Appendix D: Schedule of Meetings and Field Trips of the Working Group on the Use of Chimpanzees in NIH-Supported Research**

### **Face-to-Face Meetings and Teleconferences**

February 2, 2012: Bethesda, Maryland  
February 24, 2012: Teleconference (WebEx)  
April 4, 2012: Teleconference (WebEx)  
May 14–15, 2012: Los Angeles, California  
July 2, 2012: Teleconference  
August 1, 2012: Chicago, Illinois  
September 20, 2012: Teleconference  
October 5, 2012: Teleconference  
October 18, 2012: Teleconference (WebEx)  
November 13, 2012: Teleconference  
November 27, 2012: Alamogordo, New Mexico  
December 11, 2012: Teleconference  
December 20, 2012: Teleconference  
December 27, 2012: Teleconference (WebEx)  
January 8, 2013: Teleconference (WebEx)  
January 11, 2013: Teleconference (WebEx)

### **Presentations by Working Group Co-Chairs to the Council of Councils**

June 5, 2012: Bethesda, Maryland  
September 5, 2012: Bethesda, Maryland  
October 29, 2012: Teleconference (WebEx)  
January 8, 2013: Internet-assisted review  
January 22, 2013: Bethesda, Maryland

### **Field Trips**

The Working Group conducted several field trips to chimpanzee facilities (listed below) to observe and better understand the environments in which the animals are housed. These experiences helped Working Group members develop their definition of ethologically appropriate environments.

May 25, 2012: New Iberia Research Center, The University of Louisiana at Lafayette, New Iberia, Louisiana  
May 26, 2012: Chimp Haven, Inc., Keithville, Louisiana  
August 1, 2012: Lincoln Park Zoo, Chicago, Illinois  
November 26, 2012: Southwest National Primate Research Center, Texas Biomedical Research Institute, San Antonio, Texas  
November 26, 2012: Michale E. Keeling Center for Comparative Medicine and Research, The University of Texas M.D. Anderson Cancer Center, Bastrop, Texas  
November 27, 2012: Alamogordo Primate Facility, Alamogordo, New Mexico  
December 4, 2012: Save the Chimps Sanctuary, Fort Pierce, Florida

**Colony Management Subgroup Meeting**  
August 2, 2012: Chicago, Illinois

**Emerging Diseases Subgroup Meeting**  
December 7, 2012: Houston, Texas

## Appendix E: Summary of Expert Interviews

To assist with their deliberations concerning ethologically appropriate physical and social environments and size and placement recommendations for captive research chimpanzees, Working Group members conducted field trips to all facilities housing NIH-owned and -supported chimpanzees as well as sanctuaries housing chimpanzees that had been retired from research, entertainment, and private ownership. In addition, members of the Working Group's Colony Management Subgroup conducted a series of interviews with international experts in the care and use of chimpanzees:

- Linda Brent, Ph.D., President and Director, Chimp Haven, Inc.
- Kathleen Conlee, Vice President, Animal Research Issues, The Humane Society of the United States
- Lisa Faust, Ph.D., Vice President of Conservation and Science, Lincoln Park Zoo, Chicago, Illinois
- Paul Honess, Ph.D., Director of Animal Behaviour, Welfare, and Research, Bioculture Group, Mauritius/United Kingdom
- Sarah Long, M.S., Director, Population Management Center, Lincoln Park Zoo, Chicago, Illinois
- Elizabeth Lonsdorf, Ph.D., Adjunct Scientist, Lester E. Fisher Center for the Study and Conservation of Apes, Lincoln Park Zoo; Assistant Professor, Department of Psychology, Franklin and Marshall College
- Tetsuro Matsuzawa, D.Sc., Director, Primate Research Institute, Kyoto University
- Steven Schapiro, Ph.D., Associate Professor, Michale E. Keeling Center for Comparative Medicine and Research; Section Chief, Primate Behavior and Environmental Enrichment, The University of Texas M.D. Anderson Cancer Center
- John L. VandeBerg, Ph.D., Chief Scientific Officer, Texas Biomedical Research Institute; Director, Southwest National Primate Research Center
- Richard Wrangham, Ph.D., Ruth B. Moore Professor of Biological Anthropology, Harvard University; Co-Director, Kibale Chimpanzee Project
- Stuart Zola, Ph.D., Director, Yerkes Regional Primate Research Center

This appendix summarizes these interviews.

### **Ethologically Appropriate Physical and Social Environments**

Without exception, the experts that the subgroup consulted indicated that the most important factor for chimpanzee well-being is the ability to live and act as part of a large, complex, multi-male, multi-female social group. To maintain these social structures and provide sufficient physical and cognitive stimulation, animals should be maintained within large, complex, outdoor primary living spaces with abundant vertical and horizontal dimensions for climbing and other forms of exploration, foraging, and ranging.

Ethologists and other experts cited conditions at Gombe National Park in Tanzania, where one of the densest populations of chimpanzees live, as a possible starting point for calculating appropriate spaces. Here, the population density is approximately 0.39 square miles (0.35 km<sup>2</sup>) per chimpanzee. Chimpanzee densities at large North American sanctuaries range from 25 to 30

animals per 3–5-acre (12,000 to 20,000 m<sup>2</sup>) range. The experts consulted recognized that developing such large spaces would be impractical in most (if not all) captive research settings and that more practical densities of 1,000 to 10,000 ft<sup>2</sup> (93 to 930 m<sup>2</sup>) per chimpanzee would be more feasible, while still maintaining the ability of animal groups to appropriately range and form subgroups.

Although the experts agreed that naturalistic settings are not necessarily required for chimpanzee housing, these settings are less expensive to develop and maintain than artificial settings, and they provide a far greater range of multisensory stimulation and complexity. Functional simulations, such as artificial structures to mimic ant or termite mounds, might be added to encourage tool use and other cognitive skills development and to augment the captive physical environment.

The ethologists and other experts interviewed also emphasized the importance of management considerations for captive chimpanzees. Managing captive chimpanzees through the use of positive reinforcement training was cited as a critical means of reducing adverse stress for these animals in research and other captive settings. Furthermore, because of the importance of long-term social bonding in chimpanzees, best management practices preserve stable social groupings whenever possible.

### **Size and Placement of Future Captive Research Chimpanzees**

When asked to comment on the optimal group size for captive research chimpanzees, the scientists consulted indicated that ideally, groups should consist of at least 10 to 30 members and that larger group sizes provide more optimal cognitive stimulation for animals. The most important limiting determinant for group size is the amount and complexity of primary living space offered to chimpanzees. Based on these discussions, it was apparent that even if less than 25 to 30 chimpanzees are required annually for long-term invasive biomedical research projects, it might be necessary to hold more chimpanzees in a research facility to ensure their optimal psychological well-being. The experts also consistently recognized that noninvasive comparative behavioral and genomic research projects could be conducted using chimpanzees held in accredited sanctuary or zoo settings. The CHIMP Act (described in the glossary at the beginning of this report) permits these types of research in the federal sanctuary system.

There was no consensus regarding the specific numbers of chimpanzees required for biomedical versus comparative behavioral or genomic research. Some experts indicated that no chimpanzees are required and that all research-active and research-inactive animals should be immediately retired to a federally owned sanctuary. Other experts indicated that if chimpanzees were available for research and research funds were available from the NIH, there would be no difficulty in finding suitable projects. Importantly, it was unclear whether those interviewed believed that these new projects would be consistent with the IOM principles and criteria.

Despite this, all of those interviewed indicated that, in their opinion, the use of chimpanzees in research has declined significantly in the past decade. This was an interesting comment that is not supported by data because the number of projects using chimpanzees that the NIH has funded over the past 30 years has remained relatively constant, with sporadic increases in project

numbers from time to time (IOM, 2011, Figure 1, p. 22). Finally, several experts recognized that because of the long breeding span of chimpanzees and the broad age range of current research-active and research-inactive animals, it would not be necessary to breed chimpanzees to maintain sufficient numbers for research for at least 10 years.

## Appendix F: Summary of Public Input from NIH Requests for Information

In February 2012, the National Institutes of Health (NIH) issued two requests for information (RFIs) seeking public input into the deliberations of the Council of Councils Working Group on the Use of Chimpanzees in NIH-Supported Research. The purpose of the RFIs was to obtain broad input on issues underlying NIH's implementation of the recommendations made by the Institute of Medicine (IOM) in their report *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity* and subsequently accepted by the NIH. The first opportunity for public input was published in the NIH Guide for Grants and Contracts on February 10, 2012, as Notice number OD-12-052 ([NOT-OD-12-052](#)). An identical, second request was published in the [Federal Register](#) on February 23, 2012 to reach out to members of the public not typically reached through the NIH Guide for Grants and Contract. The comments received in response to both RFIs are summarized below.

One-hundred ten (110) comments were received in response to the RFIs. Twenty-three (23) comments were submitted on behalf of organizations while eighty-seven (87) were prepared on the submitter's behalf, or "self." Fifty-six (56) respondents submitted identical information (i.e., a form letter). The remaining fifty-four (54) comments were considered unique and were summarized.

### *RFI Comment Topic #1: Developing a plan for implementation of the IOM's guiding principles and criteria*

Respondents expressed considerable support for the IOM process, the recommendations that resulted, and the NIH's immediate acceptance of the criteria and principles for the use of chimpanzees in research. Commenters agreed that the use of chimpanzees in biomedical and behavioral research should be governed by an additional set of standards, and the reliance on chimpanzees in research should be reduced and, if possible, eliminated altogether. Differences of opinion surrounded the proposed timing to reduce their use. Some suggested immediately ceasing all research involving chimpanzees, stating that this animal model is entirely unnecessary and/or has been replaced by other methods. Others proposed to continue using chimpanzees to study specific conditions permitted by the IOM report and phase out areas of research where the chimpanzee is not necessary. It was universally accepted, however, that the housing for any chimpanzee, whether used in research, inactive, or retired, be consistent with the highest standards of care and living environments. Others believed that the Working Group should consider the ethical implications of research using chimpanzees.

Some respondents suggested that the Working Group's charge also include the option for chimpanzee retirement. Because the Working Group was charged with 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, the size and placement of retired animals is outside the purview of the Working Group. However, given the number of commenters that raised retirement as a concern and interest, those remarks are summarized in RFI Comment Topic #3.

Some commenters encouraged the Working Group to consider the financial, personnel, and other resources would likely be needed to implement the recommended oversight process, funding for alternative in vivo and in vitro models, and costs to implement recommended care and housing standards. To the extent that certain types of research would continue, respondents noted that budget support would be needed to address the bolstered psychological and physical welfare of the animals. Several commenters proposed that stopping research with chimpanzees would enable the NIH to divert those resources toward alternative models. Commenters also urged the Working Group and the NIH to increase investments in finding alternatives to the chimpanzee model.

*RFI Comment Topic #2: Factors to consider in reviewing 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. For example: criteria to assess “minimally invasive” procedures for comparative genomics and behavioral research and “ethologically appropriate” physical and social environments; criteria to balance phasing out of the existing research without causing “unacceptable losses to research programs” or an unacceptable “impact on the animals.”*

### **Ethologically Appropriate**

The IOM report states, “The animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments (i.e., as would occur in their natural environment) or in natural habitats.” Due to the uncertainty of the term “ethologically appropriate” environments, the NIH requested input on how to assess such environments.

Respondents universally were supportive of the concept of “ethologically appropriate” environments to more fully enhance the physical and psychological needs of chimpanzees. Commenters discussed the applicability of existing standards set forth by the Animal Welfare Act and various housing and environment practices as enforced by accrediting entities. Many stated, however, that “ethologically appropriate” sets a higher bar for chimpanzee habitats than existing laws and/or regulations.

Concerns surrounding the term “ethologically appropriate” pertained mainly to it lacking a definition and that, as a new concept, may not be fully represented in the terminology or site visit standards of the accrediting organization, the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), or the agency charged with federal oversight, the U.S. Department of Agriculture (USDA). Many commenters stressed the importance of defining and operationalizing “ethologically appropriate” because, by itself, the concept is subjective. Rather than provide a definition for “ethologically appropriate,” several respondents instead proposed a range of characteristics to help resolve ambiguity surrounding the term. Suggestions included:

- Accreditation from AAALAC and registration with USDA
- Environments that facilitate foraging and nesting behavior, traveling, climbing, and brachiating
- Enrichment programs that support chimpanzee problem-solving behaviors

- Social housing that supports the social needs of captive chimpanzees, including conspecific social partners
- Socially compatible grouping with a minimum group size of at least three chimpanzees to more closely approximate the size of wild chimpanzee communities; pair housing when an animal does not do well in a group
- Space for subgrouping behavior, i.e., fission-fusion social rhythm of chimpanzees
- Inside and outside housing with daily access to outside environment
- Environment free of threats or a spatial opportunity to escape threats
- Mixed-age and -gender groups

Another commenter suggested that the Working Group consider AAALAC accreditation as sufficient evidence that appropriate environments are provided.

### **Minimally Invasive and Acquiescence**

With respect to comparative genomics and behavioral research, the IOM recommended that “All experiments are performed on acquiescent animals, using techniques that are minimally invasive, and in a manner that minimizes pain and distress.” Some commenters proposed that the Working Group defer to the definition of invasive research as written in the proposed draft of the Great Ape Protection and Cost Savings Act, which states: “The term ‘invasive research’ is defined to include any research that may cause death, injury, pain, distress, fear, or trauma to a great ape.” Some respondents characterized invasivity as including methods to induce sedation, surgeries, implantation or attachment of devices, removal from “ethologically appropriate” environments or natural habitats for research purposes, and removal of blood or tissues other than what is necessary during prescribed examinations or procedures to monitor or maintain the health and well-being of the chimpanzee. Another respondent proposed to align the concept of invasive procedures with the Animal Welfare Act’s definition of major surgery, i.e., invading a body cavity. Minimally invasive procedures, in general, would be those conducted in human medicine on an outpatient basis.

Others suggested that “minimally invasive” could be described as a procedure that does not permanently alter the anatomy or physiology of the chimpanzees, such as blood collection, imaging procedures, and behavioral studies. It was suggested that some limits be placed on sedation, including the number of times a chimpanzee can be anesthetized per year for research purposes, the duration of sedation, and scheduling tests requiring anesthesia to coincide with the annual exam. Some suggested that certain laboratory tests could be minimally invasive and conducted on acquiescent animals if the chimpanzee voluntarily presented for blood draws and accepted injections for anesthesia—something that would benefit both the annual veterinary check-ups and imaging studies, for example.

*RFI Comment Topic #3: Factors to consider when advising on the size and placement of active and inactive populations of NIH-owned or -supported chimpanzees as a result of implementing the IOM recommendations. For example: ways to address capacity issues that would accompany an increase in “inactive” animals; factors to consider in transitioning the animals that are newly inactive; how many and what would be the characteristics of animals held in reserve for future research, if any; the number of animals needed to maintain a viable number of research naïve*

*animals but also genetic and social stability and sufficient diversity for unanticipated research needs.*

For purposes of this summary, the NIH clarifies that “active” means the chimpanzees are needed for current research projects that fit the IOM criteria. In comparison, “inactive” means the animal is not currently needed for research but may be needed for new projects that fit the IOM criteria. “Retired” means the chimpanzee is no longer needed for research.

### **Research “Active”**

Some respondents remarked that all chimpanzees should be retired immediately and not held in reserve for future research. Others were supportive of a limited number of “inactive” animals and diminishing numbers in “active” status. In the limited circumstances when chimpanzee use would be permissible, it was suggested that NIH-funded investigators take steps to increase the quality of life of laboratory-housed animals by working with organizations that specialize in these matters. In addition, it was recommended that facilities housing chimpanzees for biomedical research should document animal-specific plans that limit the prolonged and repeated use in research protocols and specify plans for their retirement. In addition, ongoing and regular review of the research should be conducted to assess alternative methods or models that may have emerged since the last approval.

### **Research “Inactive”**

Respondents largely were unsupportive of keeping a reserve of chimpanzees available for research; however, some were amenable to an “inactive” population if a plausible need exists and if the laboratory environment can be made more akin to the chimpanzees’ natural habitat, in effect, “ethologically appropriate.” See “Future Research.”

### **Retirement from Research**

Some commenters recommended the creation of a committee to oversee, in a transparent fashion, the retirement of chimpanzees from NIH-funded research. Respondents encouraged the Working Group to recommend a national chimpanzee management system unaffiliated with the NIH to oversee the transition of chimpanzees out of medical research laboratories and into sanctuaries. Responsibilities of this committee would include determining which chimpanzees are eligible for retirement based on predefined criteria, such as:

- Age of chimpanzee
- Medical and psychological status
- Number of years in research
- Anticipated medical and social needs after retirement that could affect the place of retirement

Proponents of retirement mostly advocated for moving chimpanzees to sanctuaries that are inspected by the U.S. Department of Agriculture and accredited by AAALAC. Most commenters lauded the sanctuary environment as a model ethology for the chimpanzee, providing ready and often unrestricted access to a foraging and forest environment, social groupings, and opportunities to exercise decision making (making choices). However, some voiced concerns about the staffing and infrastructure currently available to care for animals with chronic

conditions (e.g., HIV and advanced diabetes) and other special health and housing needs. Others expressed concerns about insufficient capacity in existing sanctuaries to house a considerable influx of newly retired animals, and new facilities would be needed to house chimpanzees retired from research and relocated to sanctuaries. Others expressed confusion over which federal laws and regulations apply to sanctuaries.

Several commenters expressed dissatisfaction with the option of retiring the chimpanzee “in place” (i.e., in the laboratory environment) versus retirement to a sanctuary largely due to concerns that the laboratory enclosures would not be “ethologically appropriate.” Others expressed that laboratory facilities, to the extent that they are not currently “ethologically appropriate,” could take steps to improve the housing and well-being of the chimpanzees. This approach could be an alternative to retiring the animals to a sanctuary. Some contended that the veterinary and diagnostic capabilities of the research laboratories are superior to those of sanctuary environments and could offer better health care to aging and possibly ill chimpanzee populations.

### **Future Research**

The IOM report suggested that a “new, emerging, or reemerging disease or disorder may present challenges to treatment, prevention, and/or control that defy non-chimpanzee models and available technologies.” The NIH asked for input on the number and characteristics of animals held in reserve for future research, if any, and the number of animals needed to maintain a viable number of research naïve animals but also genetic and social stability and sufficient diversity for unanticipated research needs. To the extent that a reserve colony is needed, it was suggested that retaining animals with breeding potential (e.g., proven breeder, good mother, mother reared, socially housed) would help maintain a self-sustaining population. It was suggested that one small colony, possibly ages 10 to 20 years old, should be retained for a brief period (e.g., five years). Other commenters separately suggested that the requirements for conducting invasive research mirror those of the Chimpanzee Health Improvement and Maintenance Protection Act (P.L. 106-551)—that is, they should offer a public comment period and mandate Department of Health and Human Services Secretarial approval for such research.

In contrast, many commenters stated that no future research on chimpanzees is necessary, and, therefore, holding a reserve population for future research is similarly unnecessary. If all chimpanzees owned by the NIH are retired, one commenter suggested that chimpanzees owned by private entities (not the NIH) could be made available for future research.

Several respondents remarked that some sanctuaries permit scientists to utilize excess specimens collected from annual veterinary check-ups and necropsy tissue for research. In addition, observational research reportedly can be conducted at some sanctuaries. The Working Group was asked by one respondent to consider allowing researchers liberal access to sanctuary populations of chimpanzees for specimen and behavioral research, should it recommend retiring some animals to sanctuaries.

*RFI Comment Topic #4: 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. For example: factors to consider in determining whether other models (e.g., in vitro, other in vivo) would be a “suitable model” for answering the research question; research areas*

*where alternative model development is recommended; whether the NIH should have a plan to maintain a minimal population of federally-owned chimpanzees and input on the design of the plan; circumstances under which chimpanzees should be considered as a model for “a new, emerging, or reemerging disease or disorder that may present challenges to treatment, prevention, and/or control that defy non-chimpanzee models and available technologies”; characteristics of the oversight committee responsible for reviewing future research proposals and determining whether they are consistent with the IOM criteria and whether they can be conducted.*

## **Review Committee for Future Research**

The IOM report recommended that “the assessment of the necessity of the chimpanzee in all grant renewals and future research projects would be strengthened and the process made more credible by establishing an independent oversight committee...” Several commenters proposed characteristics of the oversight committee responsible for reviewing future research for compatibility with the IOM criteria. Suggestions included developing a process that is transparent (i.e., open to the public and/or having a public comment period), able to be completed quickly, have committee membership composed of individuals without a personal or institutional conflict of interest, and have membership representing the following disciplines:

- Laboratory animal veterinarian for chimpanzee-specific medical and behavioral needs and to advise on the likely health effects of the research during and after the study
- Primatologist to advise on chimpanzee colony size and maintenance
- Bioethicist and member of an institutional review board to provide input on the ethics of conducting the proposed research in humans
- Public health official to advise on whether foregoing the use of chimpanzees in research would result in significant delays in making medical advances for life-threatening or debilitating conditions
- Statistician to advise on the statistical power of the number of animals proposed for use
- Technologists and other experts in alternative methods and models
- Virologist to advise on hepatitis C virus biology
- Immunologist with expertise in monoclonal antibody development
- Social scientist/neuroscientist for insights into whether proposed behavioral research would provide unattainable insights into behavior, mental health, emotion, or cognition
- Geneticist specializing in comparative genetics and transgenic models
- Patient advocates representing areas of research proposed for study
- Member of the public

Another respondent recommended having a chimpanzee institutional animal care and use committee (IACUC) at the national or regional level to oversee their research use. Some commented that the existing NIH scientific peer review process could serve to review research applications proposing to use chimpanzees in research because the vertebrate animal section of grant applications could contain the requested details. As an outcome of these reviews, one commenter suggested that if an application is denied because alternatives exist, the investigator may need options for learning how to utilize the alternative model or method.

## **Alternatives**

Respondents were universally supportive of exploring alternative methods for studying diseases and conditions and emphasized the importance of continuing to study, develop, and commit resources to finding alternatives to the chimpanzee model. Several commenters who discussed alternatives also remarked that the development of new or novel methods might be hampered by continuing to use chimpanzees in research, suggesting that there would be little incentive to find alternatives so long as the chimpanzee model is available. Others posited that suitable alternative models are already currently available and should obviate the need for any further research using chimpanzees, even in the areas the IOM suggested were appropriate to continue. Several commenters suggested making available to researchers and the review committee a reference list of suitable alternatives to the chimpanzee model.

## **Other Comments**

Some respondents debated the conclusions of the IOM report with respect to the hepatitis C virus and monoclonal antibodies, asserting that chimpanzees are not a good model of human disease and existing alternative methods and models obviate a role for chimpanzees in research. Others stated that chimpanzees cannot give informed consent and, therefore, should not be used in research. In contrast, several others presented comments strongly favoring the use of chimpanzees to study the hepatitis C virus, for example, and offered additional rationale as to why this research should be continued.

One commenter disagreed with the NIH Guide Notice announcing the policy on NIH research involving chimpanzees ([NOT-OD-025](#)), suggesting that the NIH should accept and review grant applications proposing to use chimpanzees in research pending the establishment of the formal oversight process. This commenter suggested that not allowing grant application reviews in the interim penalizes the investigator seeking NIH funding.

Several comments were largely supportive of research involving stored biological samples, specimens collected passively from the chimpanzee habitat (e.g., feces), specimens resulting from annual veterinary check-ups, and observational research where no interaction with the chimpanzee takes place. One commenter was opposed to obtaining new material for research without scientific justification as to why the existing and stored materials are unsuitable.

# Appendix G: White Paper on the Use of Chimpanzees in New, Emerging, and Reemerging Diseases Research

## Executive Summary

The five-member Emerging Diseases Subgroup of the Working Group (WG) on the Use of Chimpanzees in NIH-Supported Research was charged with advising the WG on whether and how chimpanzees will be needed in the future for research involving infectious diseases. The Subgroup reaffirmed Recommendation 1 in the Institute of Medicine/National Academy of Sciences (IOM) report by the Committee on the Use of Chimpanzees in Biomedical and Behavioral Research (IOM, 2011). This recommendation states that the National Institutes of Health (NIH) should limit the use of chimpanzees in biomedical research to those studies (1) for which there is no other suitable model available for the research in question; (2) the research in question cannot be performed ethically in 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. With regard to infectious disease research, the IOM Committee considered only two research areas that might be necessary, hepatitis C virus vaccine research and the “unknown-unknown” (i.e., a lethal new, emerging, or reemerging infectious agent or a novel bioterrorism agent for which all other approaches to develop prevention and control strategies have failed, an exception also referred to as the “safeguard clause”).

***Scientific rationale for using chimpanzees in infectious disease research.*** The Subgroup agreed that only in a unique and rare situation would infectious disease research warrant use of chimpanzees. This would have to be a case in which the public health need outweighed the issues involved in using chimpanzees in high biocontainment (i.e., animal biosafety level [ABSL] 3 and 4 laboratories) facilities. It was presumed that only a new, emerging disease of exceptional lethality would warrant any chimpanzee use. Following a decision that chimpanzee use would be warranted, several practical questions come into focus: (1) the availability of chimpanzees that are suitable research subjects, (2) the availability of staff trained in both chimpanzee veterinary care and high biocontainment research, (3) appropriate ABSL3 and/or ABSL4 facilities that could be used for such work, (4) chimpanzee usage and biosafety regulations that would allow such work, and (5) the substantial financial resources required for such research. This scenario would be predicated on evidence that the new emerging disease could not be adequately studied in other experimental animal species or by using conventional microbiological/virological laboratory techniques. There has been full agreement that chimpanzees would not be used for discovery-phase research and that the need might only arise in downstream research (e.g., in pathogenesis/pathophysiology research required for preclinical vaccine or drug development research).

***High biocontainment facility considerations.*** There never has been any research employing chimpanzees under high biocontainment (ABSL3, ABSL4) conditions. In the case (rare as it may be) of a naturally occurring outbreak or bioterrorism event involving an unknown-unknown, several options would have to be considered since none of the current high biocontainment facilities were designed to house chimpanzees. (1) An existing ABSL3/4 facility that is in close proximity to a chimpanzee research facility might be adapted for use. (2) NIH could, in

partnership with a federal ABSL4 facility, build modifications so as to house chimpanzees. This would be most feasible if the federal facility were still in a planning phase at the time of the decision. The Subgroup was only aware of one such facility, the new U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) BSL4 facility at Fort Detrick, Maryland. (3) NIH could build a new ABSL4 facility specifically designed to house chimpanzees. Since all high biocontainment facilities are designed around the number and size of animals that are to be housed, this option would yield the best facility. This is by far the most expensive option, as BSL4 construction costs are currently estimated to be approximately \$6,100 per net square foot, and annual operating costs are 16% of construction costs. Maintaining unused laboratory facilities is impractical and cost-prohibitive, so this option would have to include plans for alternative interim use of the chimpanzee laboratory. (4) NIH could choose to take no action, given that the need to use chimpanzees in high biocontainment facilities is very unlikely.

***Availability of research chimpanzees.*** Clearly, options 1–3 above assume that research chimpanzees would be available at the time of a national emergency. There are no active breeding programs at any of the five U.S. national chimpanzee research facilities. Decisions made regarding the need for chimpanzees for the described purposes would determine whether or not there will be chimpanzees available for use in timely fashion, should the need arise. If the recommendations of the IOM Committee are accepted in full, in the near future, all invasive medical research using chimpanzees supported by NIH funds would end, with the two exceptions already cited. This would bring the United States into a consistent regulatory framework with the European Union and other countries. Hence, it is likely that there would not be any research animals in reserve, even in the case of a national emergency in which the “safeguard clause” would allow the use of chimpanzees

### ***Overview of Activities and Conclusions of the IOM Committee in *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity Regarding Emerging Diseases****

When a new or emerging infectious disease is suspected, a complex continuum of prevention and control activities may be called into action, but, given financial and resource constraints, decisions must be made and priorities set. The full continuum (sometimes called the “discovery-to-control continuum”) comprises many activities and resources, which may be divided into investigative and interventional (or translational) phases (Murphy, 1998). NIH’s role, through its intramural and extramural programs in this discovery-to-control continuum, typically begins immediately after a novel dangerous pathogen has been identified, but this is a complex subject with many variables. The sequence of events is typically as follows: (1) identify the pathogen, usually by genomic sequencing, to determine if it is new or related to any known pathogen; (2) determine whether existing knowledge from a known pathogen can be bridged to the new pathogen; (3) use sequence data to develop diagnostic tools; (4) isolate the pathogen and undertake in vitro studies; (5) undertake modeling studies in parallel with non-chimpanzee animal studies; and (6) determine if animal models are needed to study pathogenesis or develop drugs and vaccines, and ensure that the model recapitulates the disease observed in humans.

Three guiding principles were developed by the IOM Committee on the Use of Chimpanzees in Biomedical and Behavioral Research:

1. 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.
3. The animals used in the proposed research must be maintained either in ethologically appropriate physical and social environments or in natural habitats. (It was understood in general that high biocontainment research is not "ethologically appropriate.")

The scientific rationale for using chimpanzees in infectious disease research was discussed at length by the IOM Committee. It is recognized that chimpanzees do not play a role in discovery-phase infectious disease research. There are several reasons for this: (1) over the years, chimpanzees have proven to be quite resistant to many pathogens, whereas in discovery research, the need is for animal models that are relatively susceptible to infection with the infectious agent of concern; (2) there is an early need to use large numbers of susceptible animals to measure many variables quantitatively; and (3) we have high confidence in modern molecular biological technologies for agent discovery and initial agent characterization. If chimpanzees are needed for research with an unknown-unknown, it would be in later-stage investigations of the disease outbreak, such as for pathogenesis research during vaccine/drug preclinical development. The likelihood of needing chimpanzees for research on an unknown-unknown is unknown but presumed to be very low since in all of the zoonoses identified to date, a suitable animal model other than a chimpanzee has been identified.

In general, the mantra for dealing with new, emerging, or reemerging infectious diseases is "we cannot predict, but we can prepare" (Nancy Cox, Director of the World Health Organization's World Reference Center for Influenza at the Centers for Disease Control and Prevention [CDC], personal communication to Frederick A. Murphy). Seventy-five percent of human pathogens have been zoonotic, and 9 out of 10 naturally acquired diseases in the last 20 years have been zoonotic. As noted in the IOM report, *Learning from SARS: Preparing for the Next Disease Outbreak* (Knobler et al., 2004), we must anticipate the emergence of new zoonoses. The strategies for containing known zoonoses will serve as models for containing new, unknown ones. It is in this context that the need for housing chimpanzees in a high biocontainment facility must be considered. The question of where NIH falls in the universe of responsibilities to respond to any particular emerging infectious disease threat does not lend itself to a simple answer. There are lessons from how disease outbreak events have been managed historically. Indeed, NIH has played a major role in many such investigations. Today, we may say that the Department of Homeland Security deals with threat assessments, the CDC is responsible for responding in the field to emerging pathogen threats, and the Food and Drug Administration (FDA) approves vaccines and drugs for intervention. NIH's portfolio of intra- and extramural programs encompasses a wide range of activities that cut across the missions of all the other agencies; lead responsibility within the biomedical research realm; and major responsibilities extending into areas of education, training, international field research, and countermeasure development.

If it is decided by NIH to respond to the IOM Committee's report on the use of chimpanzees in biomedical and behavioral research with the development of a new high biocontainment chimpanzee facility, perhaps, given the strategic decision to build the "National Interagency Biodefense Campus" in Frederick, Maryland, there is an opportunity for a partnership between NIH and USAMRIID to construct a common facility. Given that NIH already has its Integrated Research Facility on that campus and that the new USAMRIID facility is still in the design phase, there is a sense of practicality in this notion.

In Europe, the special situation of needing to use chimpanzees for emerging infectious disease research is covered in a "safeguard clause" in European Union regulations (Article 55 of Directive 2012/63/EU of the European Parliament and of the Council; September 22, 2010). The likelihood of needing to use this clause for dealing with a lethal disease caused by an unknown-unknown pathogen is difficult to assess. Since the safeguard clause has never been employed and European Union documents do not go into exhaustive detail, it is not known if the clause could be practically implemented for short-term use (up to months), much less for longer-term research (years).

### **1. Are all emerging diseases caused by infectious agents and do all emerging infectious diseases "emerge" from animal reservoirs?**

The term "emerging disease" may refer to any disease, infectious or not, but in common usage it has been limited to infectious diseases, as first used by Joshua Lederberg and his colleagues in the seminal IOM report, *Emerging Infections: Microbial Threats to Health in the United States* (Lederberg et al., 1992). Although the term might best be limited to diseases whose incidence has increased within the past two decades and to diseases that threaten to increase in the near future, in some contexts, it has been extended to all but the most endemic infectious diseases. To date, approximately 75% of emerging infectious diseases have been zoonotic in origin, and about 25% of these derive from nonhuman primate host species. The zoonotic transmission pattern involves transmission to humans from an ongoing reservoir life cycle in animals or arthropods without the permanent establishment of an independent life cycle in humans. It is useful to distinguish this pattern from "species jumping" transmission (i.e., host range extension) where initial transmission to humans is from a reservoir life cycle in animals, followed by the establishment of a new life cycle in humans that no longer involves an animal reservoir.

It is impossible to predict how often an "emergence" event will take place and whether or not it would involve chimpanzees. Many human pathogens originated in animals (e.g., measles virus, influenza viruses). Products of animal origin may also serve as sources for zoonotic or species-jumping pathogens. Many animal species have been involved in the emergence of human infectious diseases. Wild (e.g., bats, rodents) as well as domestic (e.g., horses, cats) and food (e.g., poultry, cattle) animals have been implicated.

Both NIH and CDC have lists of "priority emerging pathogens" that are periodically reviewed and are subject to revision in conjunction with federal partners. The role of the National Institute of Allergy and Infectious Diseases (NIAID) is to conduct and support research designed to learn as much as possible about new or emerging infectious agents and the infections they cause in order to develop tools for identification, diagnosis, treatment, prevention, and control of such

pathogens. In recent years, NIAID has moved toward a broad-spectrum approach for translational research to advance each of these areas; this research often incorporates sophisticated genomic and proteomic technologies, including novel animal model technologies.

## **2. Would chimpanzees be expected to be an animal reservoir for human infectious disease?**

Possibly. Chimpanzees are infected with many bacterial, viral, fungal, and parasitic agents that may be transmitted to humans. Fifty-two infectious agents of humans have been identified in chimpanzees according to the Global Mammal Parasite Database (17 protozoa, 13 helminths, 16 viruses, 5 bacteria, and 1 fungus; Cooper et al., 2012), but there are other examples suggesting that the database is not yet complete. Two important considerations are the possibility of transmission of infectious agents to humans via the bush-meat trade in Africa and the proven transmission of nonhuman primate viruses to staff in primate centers.

The most notable example of viral host species jumping is the SIVcpz virus that moved from chimpanzees to humans to become HIV-1. There are several other examples of transmission of pathogens from chimpanzees to humans, including monkeypox (BSL3), Ebola virus (BSL4), and several respiratory pathogens. Significantly, chimpanzees have not been directly exposed to highly virulent infectious pathogens for the development of drugs and vaccines, even in the case of Ebola and monkeypox viruses; rather, smaller animal models have been used.

## **3. What is possibility of a human pathogen “jumping” to chimpanzees, and could such a pathogen then jump back to humans in a more virulent form?**

There is evidence for human pathogens jumping to chimpanzees. However, the evidence that infectious diseases in chimpanzees can jump to humans makes this an important question. A respiratory disease, suspected of having been transmitted by humans to wild chimpanzees in the Tai National Park in the Côte d'Ivoire, involved endangered chimpanzee populations, which have suffered dramatic population declines from pathogens shared with humans, including respiratory syncytial virus and human metapneumovirus (Köndgen et al., 2008). In another study examining serum from 14 captive chimpanzees in Japanese primate research institutes, antibodies against 29 of 61 human pathogens tested were detected at high or low prevalence in the chimpanzees (Kooriyama et al., 2013). Drug-resistant human *Staphylococcus aureus* has been detected in sanctuary-housed chimpanzees and among veterinarians working in the sanctuaries (Schaumburg et al., 2012). Data from a longitudinal analysis of measles antibody responses in 45 non-human primate care workers for a period of up to 26 years (Amanna et al., 2007) demonstrated that virus jumping does occur. All of the subjects worked at the Oregon National Primate Research Center. There were spikes in antibody titers in four samples from 1999 during an outbreak due to a primate paramyxovirus in the nonhuman primate colony. The antibody spikes identified in these four human subjects appear to represent uncharacterized simian paramyxovirus infections that cross-reacted with measles antigens in the serological assays. Fortunately, the infections were inapparent and there was no indication of human-to-human spread. This is not the first time that viruses have spread from nonhuman primates to humans; there are a number of cases in which this has happened in the past. For example, in 1966, there were outbreaks of tanapox virus that

occurred in three primate centers in the United States, and some animal handlers were infected through skin abrasions (Downie and Espana, 1972).

#### **4. Can you predict how often an “emergence” event would take place?**

No. We cannot predict how often an emerging infectious disease episode might occur. We never have done so in the past, and it is unlikely we would in the future, even with modern methods. We should expect the unexpected and be prepared. Modeling studies are now being used to assess emergence, and evolutionary biologists are using phylogenetic host specificity to help us understand why some parasites or microbes are shared among primates (Cooper et al., 2012). The idea of “pathogen flow” from humans to monkeys, and possibly from monkey to monkey, including wild apes, is being considered and investigated (Nunn and Hare, 2012). Whether such “flow” might result in a future emerging infectious disease event, as humans continue to encroach on wildlife habitats, remains to be seen. “Hotspot” maps can be generated to show the evolutionary relationship between pathogen sharing and divergence time between primate species; these maps highlight regions where the risk of disease transfer between wild primates and from wild primates to humans is greatest (Pedersen and Davies, 2009). The authors suggest Central Africa and Amazonia as potential future hotspots for cross-species transmission events between wild primates, due to the presence of diverse, closely related primate species. In addition, hotspots for host shifts to humans are most likely in the forests of Central and West Africa, where humans come into frequent contact with wild primates. It has been suggested that these areas are also most likely to sustain a novel epidemic due to their rapidly growing human populations. However, such studies also have critics, who contend that they lack geographic precision, at least at present.

The rise in ecotourism is also providing environments for increased interactions among humans and wildlife. At present, we have little evidence regarding the potential importance of this trend. The response to an episode of disease stemming from ecotourism may well be driven by severe morbidity and mortality rates, given the high cost of surveillance and control strategies.

History has shown that it is likely that some emerging disease or biodefense threats will be unexpected and caused by a new or emerging pathogen. Current modeling efforts are skewed toward predicting outbreaks of known pathogens and are not very good at predicting events caused by an unknown-unknown infectious agent. As stated above, no emerging disease threat has ever been accurately predicted.

#### **5. How would chimpanzees be used in an emerging disease scenario?**

Small animal models (i.e., mice, rats, hamsters, guinea pigs, rabbits, and nonhuman primates) would normally be tested first, and then research might potentially move to nontraditional laboratory animals, such as ferrets or livestock, depending on the source or circumstances of the outbreak. Priorities for using different animal host species would likely be identified based on analogies to similar pathogens that have been studied in the past. For example, an emerging disease episode caused by a new orthopoxvirus would likely call for experiments in small rodents, rabbits, or macaques. Unless the episode involved direct chimpanzee-to-human spread, it is unlikely that chimpanzees would even be considered. The exception might be an emerging

disease in wild chimpanzees that threatened the survival of the species in the wild; planning for such an intervention is ongoing in West Africa.

Chimpanzees are our closest biological relative among the nonhuman primates, and they share a close evolutionary and physiological relationship. In the past, this was the basis for rationalizing that chimpanzees must be valuable models for human diseases. For example, it was thought that the ability to infect chimpanzees with HIV-1 might be critical for developing an understanding of the basic biology of the disease and for drug and vaccine development. The same was also true for hepatitis B and C, again in the context of the era. However, after testimony from many experts, the IOM Committee concluded that with the exception of hepatitis C vaccine research, advances in medical science and technologies have obviated the need for chimpanzee research. As stated above, the other exception is the unknown-unknown, and the Emerging Diseases Subgroup concurred with this conclusion, again based on unpredictable practicality of usefulness and not on the genetic and physiologic relationship between humans and chimpanzees.

#### **6. How many animals of what sex and age would be needed for infectious disease research in chimpanzees under high biocontainment conditions?**

Most emerging infectious diseases of clinical relevance infect both males and females equally, so either sex of animals could likely be used. The age range called for would depend on susceptibility and would be model specific. In humans, an inverse bell curve exists for most viruses (flu, measles, varicella zoster virus, smallpox, etc.), with the very young and the elderly being more susceptible than young adults.

The number of animals needed would depend on the frequency with which a disease causes pathology or clinical presentation of interest such as rash, fever, illness, death, etc. For example, yellow fever virus has a high mortality rate (up to 20% in humans and up to 100% in rhesus macaques), whereas other closely related flaviviruses, such as dengue viruses, have a mortality rate of approximately 0.1% in humans and are not typically lethal in macaques. In the latter example, a different measure of infection is needed (such as immunological host response measures), and still, because of individual variation, large numbers of monkeys are often needed to provide statistically significant data. In a 1973 study that has been widely accepted in developing a working immunological correlate for protective immunity following yellow fever vaccination, 68 monkeys were required (Mason et al., 1973). In another study confirming that neutralizing antibody is both necessary and sufficient for protective immunity against lethal monkeypox infection, 23 monkeys were used (Edghill-Smith et al., 2005). These examples serve to demonstrate that large numbers of chimpanzees might be needed for any study, especially a study of the immunological response, such as a vaccine efficacy study.

In conclusion, there is no set number of animals that would be required for a definitive study; it really depends on the model's purpose, but many experiments in animal models are only valuable when a rather large number of animals is employed.

#### **7. What is the timeframe for responding to an emerging disease?**

If all other animal models fail and a decision is made that chimpanzees are needed to resolve key issues in dealing with a deadly new or emerging infectious disease, the call would be for urgent, immediate use. As time passes and ongoing research indicates a need for chimpanzee use, events may rapidly escalate, leading to a timeframe that can only be met by having all resources, facilities, animals, and personnel at the ready. This reality and the dilemma it presents are explained in more detail elsewhere in this document.

#### **8. Is there a need for a chimpanzee model for emerging diseases or would other models suffice or be at least as good?**

There are many animal models that are used to study emerging infectious diseases, with rodents (mice, rats, hamsters, guinea pigs) being most commonly used. Examples of non-standard small animals include deer mice, prairie dogs, gerbils, and many others. Today, genetically deficient mice (e.g., SCID, AG129, STAT1 KO) and genetically modified mice (e.g., humanized mice) play an ever-increasing role. Nonhuman, non-chimpanzee primates that are used in research include macaques (e.g., cynomolgus, rhesus, Japanese) and other African, Asian, and South American monkey species. Each species differs in susceptibility to different infectious agents (e.g., simian varicella virus, simian immunodeficiency virus). One would have to decide where chimpanzees fit into the overall project and at what point they would be used. For pathogenesis models, it may be possible to make analogies with human autopsy data.

New animal models are being developed continually. There has been a shift away from traditional models and toward models employing highly manipulated animals. Nevertheless, pathogenesis studies still require animal models. Persistent, chronic, and recrudescing diseases pose unique challenges and require even more sophisticated manipulations of animals as models.

For rare but serious diseases, product-driven studies may need to consider the FDA Animal Rule. This greatly raises the expectations for the applicability of animal model studies and would raise expectations about the true value of data from chimpanzee experiments. For example, the combination of animal and strain of pathogen used would likely be selected so that lethality occurred in untreated animals but not in treated animals. If a decision were made to use chimpanzees, it might be necessary to use staged experiments with smaller numbers of animals per study along with data accumulated from multiple studies. Whether the FDA Animal Rule would accommodate this is unknown.

#### **9. Are other animal models in development that would change the potential need in 5 years, 10 years, or beyond?**

Yes, there will always be new models, and they may be developed by testing different pathogens in different species of hosts, as mentioned previously. Mouse models will be developed based on genetic crossing or genetic engineering that will provide new potential for allowing pathogen replication and pathogenesis. Examples of these new strains include knock-in mice with human receptors for specific viruses, knock-out mice with higher susceptibility to infection, humanized mice, and xenotransplanted mice as well as any number of combinations derived by breeding different genetically altered mice. In addition, new non-human primate models and other non-murine animal models are being developed.

**10. Could animals be retrieved from a sanctuary or must they be ready for immediate use in a research facility?**

No. Chimpanzees for future infectious disease research would have to be held in research facilities that can provide optimal veterinary care and behavioral training to support research activities.

It should be noted that Chimp Haven (Keithville, Louisiana) is the only NIH-supported sanctuary. The Chimpanzee Health Improvement Maintenance and Protection Act of 2000 [PL 106-551 (HR 3514)] originally specified that animals could be returned to research in case of a health crisis, but in 2007, the Chimp Haven is Home Act [PL 110-170 (S 1619)] was passed and prohibits chimpanzees retired from medical research to be returned to laboratories. Even if the prohibition against the removal of chimpanzees from the sanctuary were eliminated, there would be factors to consider when returning chimpanzees from sanctuary populations to active research. First, research animals must be very well characterized in terms of health histories and current physiological status. It would need to be verified that the chimpanzees brought from sanctuaries are routinely characterized for health-related characteristics as they are in research facilities.

Secondly, the chimpanzees in sanctuaries would need to be trained in routine research-related procedures as they are in research facilities. The chimpanzees maintained in research facilities are subjected to daily training, so they cooperate with routine research-related procedures. Training in research-related procedures includes sedation, oral and injectable dosing, and presentation of body parts for examination. Chimpanzees are also trained for urine donation and transfer between indoor and outdoor enclosures. This training minimizes the stress associated with participation in studies and maximizes the quality of research data generated from the animals. Training also maximizes the safety of routine research procedures both for the chimpanzees and their human caretakers.

There are arguable advantages to maintaining chimpanzees for future research needs at research facilities, if such a decision is made. Because they are already on site, the chimpanzees are immediately available for research and are not subjected to trauma associated with removal from one facility, transportation to a new facility, and integration into a new facility. Furthermore, chimpanzees in research facilities are fully characterized for research, facilitating their selection for research protocols. Finally, and very importantly, research chimpanzees are accustomed to animal care staff, research staff, and standard research procedures.

**11. Could a research facility in the United States undertake studies with chimpanzees under high biocontainment (ABSL3 and/or ABSL4) conditions?**

a. Veterinary Perspective

To date, no research involving chimpanzees in high biocontainment conditions has ever been done in the United States. If such studies were undertaken in a high biocontainment facility, a minimum of 8 weeks would be required to get standard operating procedures in place for the care

and use of chimpanzees in high biocontainment conditions. If chimpanzees were being transported from another facility, there could be an additional 30-day minimum quarantine period. Animals would also need to be acclimated and psychologically evaluated before being put into high biocontainment facilities.

If chimpanzees were to be used in any research on an unknown-unknown or a unique bioterrorism threat agent, proactive laboratory assessment of “background flora” (i.e., infectious agents endemically or episodically present in chimpanzees) would be necessary, and this would require additional resources. In the past, these issues have plagued nonhuman primate research, but these important considerations have often been ignored by the scientific community. In contrast, laboratory mice are tested regularly for all known murine viruses and microbes to insure that they are “pathogen free.”

#### b. Biocontainment Perspective

None of the high biocontainment facilities that currently exist in the United States were designed for use with chimpanzees. The design process for high biocontainment facilities includes a user scientific committee to review the appropriate animal models that will be used in the facility, instrumentation needed, decontamination systems that will be used, and other similar considerations. There is also input from the peer-review process, in which the size and numbers of animals to be used are set historically for the design of the building. There are also numerous safety and security regulations from national bodies.

Recent design processes for high biocontainment laboratories operated by NIH, the Department of Homeland Security, and the Department of Defense established the maximum weight of primates that could be used as 8 to 10 kilograms, appropriate for the upper size of an adult rhesus macaque. It was noted that a chimpanzee at birth weighs approximately 2 kilograms, an adult female weighs approximately 30 to 40 kilograms, and a full-sized adult male can weigh up to 150 kilograms. Large animals require larger caging (at least 25.2 square feet for animals over 10 kilograms); this requirement can be overruled by attending veterinarians and the Institutional Animal Care and Use Committee if there is a critical emergency. The maximum size of the animal rooms within the current ABSL3 and ABSL4 biocontainment facilities is approximately 300 square feet. These configurations also determined the size of all the supporting scientific and biocontainment equipment (including caging) that is/will be used in the facilities (e.g., imaging equipment for a 10-kilogram animal). One also has to be sensitive to the fact that if chimpanzees are brought into an existing high biocontainment facility, all other studies would likely cease, including critical experiments already in progress.

### **12. What facilities would be needed to undertake studies with chimpanzees under high biocontainment conditions?**

Decisions made regarding the size and number of animals that will be housed in a biocontainment facility affect both biocontainment and scientific considerations. From a biocontainment design perspective, the sizes of the rooms and numbers of animals that will be used determine the barrier decontamination capabilities of the facility (i.e., autoclaves, pass-through fumigation chambers, dunk tanks); breathing air capacities in the BSL4 suites; heating,

ventilation, and air conditioning capabilities in the BSL3 and BSL4 facilities; effluent and carcass disposal systems and procedures; and animal watering systems. The size and number of animals also determines the size of imaging equipment (MRI, PET scanner), aerobiology equipment, and Class III aerobiology isolation equipment; the size and equipment in the necropsy, procedure, and surgical suites; storage capabilities; and the dimensions and design of animal caging.

ABSL3 facilities intended to house chimpanzees should be designed at a minimum to comply with the standards set forth in the U.S. Department of Agriculture ARS-242.1 manual (U.S. Department of Agriculture, 2012). These standards provide the necessary personnel and environmental protection required for BSL3 agents on NIAID's List of Emerging and Reemerging Diseases, which includes Category A, B, or C priority pathogens. ABSL4 facilities should have similar designs to the facilities currently available in the world for the support of agricultural programs. The facilities in Winnipeg (Canada), Gelong (Australia), and Madrid (Spain) have large-animal rooms, but these rooms are small and are not suitable for chimpanzee work. All of the barrier support in these facilities is designed for livestock, and carcass/waste disposal systems are robust enough to handle animals the size of chimpanzees. ABSL4 facilities are purpose built, and one cannot upgrade an ABSL3 facility to create a ABSL4 facility. Facilities that house chimpanzees should have holding/acclimation and quarantine facilities (that are ABSL2 certified) separate from the high biocontainment facility, which reduces costs since there are different building requirements for ABSL4 facilities. Cage storage is also a major consideration, even if collapsible caging is used. From engineering and facility perspectives, it is a significant scientific and financial venture to consider using chimpanzees in emerging infectious disease research.

In the case of an unknown-unknown pathogen, it would be difficult to distinguish between ABSL3 and ABSL4 conditions for chimpanzee experiments, so one should assume that ABSL4 containment is required.

The number of animals used per study depends on the disease; however, for an individual experiment involving four chimpanzees in high biocontainment conditions at any one time, rooms should be at least 1,000 square feet in size to accommodate the cleaning and manipulation of squeeze-back panels in the cage system. Two such independent rooms would be considered ideal, as this would enable active ABSL4 work with four animals while the next four animals were being acclimated to the ABSL4 environment. Once ready, the active room can be cleaned and decontaminated while the second group undergoes active studies. Alternatively, a separate BSL2 room within the ABSL4 facility could be used to hold the four animals waiting to go into active studies in the ABSL4 laboratory. The facility should be constructed with an independent chemical shower, suit room, body shower, and clean change area. There should be an adjoining procedure/necropsy room equipped with a biological safety cabinet, necropsy and procedure table large enough for a chimpanzee, and an autoclave large enough to process the carcasses and the panels of the collapsible caging. It should be emphasized that the above example is hypothetical as there has been no research employing chimpanzees under high biocontainment conditions and none of the current ABSL4 facilities was designed to house chimpanzees.

### **13. Could animals be returned to a sanctuary after the studies have been completed?**

Chimpanzees could not be returned to a sanctuary given current guidelines and requirements that animals used in ABSL-3 or -4 experiments must be euthanized at study end. ABSL3 and ABSL4 nonhuman primates held in ABSL3 facilities have been repurposed and have been held for other ABSL3 experiments, but they never leave biocontainment.

There was discussion as to whether or not it would be possible to bring animals out of ABSL3 or ABSL4 housing. With appropriate markers of viral clearance (PCR and neutralizing antibody) followed by an appropriate safety period, animals could be sanitized in decontamination rooms and moved to BSL2+ containment housing for a further monitoring period. There would be major considerations for a decontamination procedure for bringing a chimpanzee out of high biocontainment housing as it would have to be validated; would only work for acute, short-duration diseases; and would have to be approved by regulatory agencies. It is considered very unlikely that the regulatory agencies would approve such protocols based on current regulations. It is more likely that other non-chimpanzee models would be available, as there are good nonhuman primate models for all known pathogens.

Taking an animal into an ABSL4 facility is considered terminal—all experiments require animal euthanasia at study end. The time an animal spends in an ABSL3 or ABSL4 facility is usually minimal because these facilities are so expensive to operate.

The Subgroup discussed whether the United States should invest in an ABSL3/4 facility for chimpanzees, given that this type of research has never done before and current high biocontainment facilities were not built to undertake chimpanzee studies. Resolution of this question would have to involve further discussion by experts and policy authorities. If a high biocontainment laboratory were to be built, plans would need to be made to maintain the facility. These laboratories are extremely expensive to run regardless of *whether they are empty or in use*. The construction costs for ABSL4 facilities are approximately \$6,100 per assignable square foot and there are additional support facilities and security facilities that add to core construction and commissioning costs. It takes a minimum of 5 years to build an ABSL4 facility from scratch. Annual maintenance costs are 16% of construction costs. Maintenance requires highly skilled mechanics and engineers.

Other facility-related issues involve (1) the equipment and staffing requirements that must be in place, (2) the funding priority for such “stand-by” research resources, (3) the costs of long-term maintenance of facilities, and (4) regulatory and oversight authority. The U.S. Department of Defense, Department of Homeland Security, and Department of Health and Human Services may be involved with chimpanzee research, but it is not at all clear which federal agencies (e.g., the CDC, NIH, USAMRIID) would be in charge of or willing to maintain stand-by facilities. Given that these agencies have different missions, consideration of which agency might provide the best leadership might depend on whether the use of chimpanzees involves pathogen discovery or downstream vaccine/drug development research.

Historically, most nonhuman primate experiments performed at ABSL4 or ABSL3 facilities have been of very short duration (i.e., weeks), whereas many chimpanzee protocols carried out at

ABSL2 facilities last for months or years (e.g., hepatitis B and C research). Scientists in the United States have no experience with longer-term research employing chimpanzees in high biocontainment facilities and certainly no experience in the intermittent use of such a facility when the need arises. In addition, all animal infectious disease experiments done at ABSL3 and ABSL4 facilities involve euthanasia of all subject animals. The public response to this requirement for experiments involving chimpanzees must be considered. All chimpanzee experiments done in the last 20 years have been survival experiments involving BSL2 infectious agents, and most animals have been used for multiple protocols (e.g., HBV, HCV, HIV-1); funding for these experiments has included the cost of lifetime care.

## References

Amanna IJ, Carlson NE, Slifka MK. Duration of humoral immunity to common viral and vaccine antigens. *N Engl J Med.* 2007 Nov 8;357(19):1903-1915.

Cooper N, Griffin R, Franz M, Omotayo M, Nunn CL, Fryxell J. Phylogenetic host specificity and understanding parasite sharing in primates. *Ecol Lett.* 2012 Dec;15(12):1370-1377.

Downie AW, España C. Comparison of Tanapox virus and Yaba-like viruses causing epidemic disease in monkeys. *J Hyg (Lond).* 1972 Mar;70(1):23-32.

Edghill-Smith Y, Golding H, Manischewitz J, King LR, Scott D, Bray M, Nalca A, Hooper JW, Whitehouse CA, Schmitz JE, Reimann KA, Franchini G. Smallpox vaccine-induced antibodies are necessary and sufficient for protection against monkeypox virus. *Nat Med.* 2005 Jul;11(7):740-747.

Institute of Medicine. *Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity.* Washington, DC: The National Academies Press, 2011.

[http://www.nap.edu/catalog.php?record\\_id=13257](http://www.nap.edu/catalog.php?record_id=13257)

Knobler A, Mahmoud A, Lemon S, Mack A, Sivitz L, Oberholtzer K; Forum on Microbial Threats, Board on Global Health. *Learning from SARS: Preparing for the Next Disease Outbreak: Workshop Summary.* Washington, DC: National Academies Press; 2004.

[http://www.nap.edu/catalog.php?record\\_id=10915](http://www.nap.edu/catalog.php?record_id=10915)

Köndgen S, Kühl H, N'Goran PK, Walsh PD, Schenk S, Ernst N, Biek R, Formenty P, Mätz-Rensing K, Schweiger B, Junglen S, Ellerbrok H, Nitsche A, Briese T, Lipkin WI, Pauli G, Boesch C, Leendertz FH. Pandemic human viruses cause decline of endangered great apes. *Curr Biol.* 2008 Feb 26;18(4):260-264.

Kooriyama T, Okamoto M, Yoshida T, Nishida T, Tsubota T, Saito A, Tomonaga M, Matsuzawa T, Akari H, Nishimura H, Miyabe-Nishiwaki T. Epidemiological study of zoonoses derived from humans in captive chimpanzees. *Primates.* 2013 Jan;54(1):89-98.

Lederberg J, Shope RE, Oaks SC, Jr; Committee on Emerging Microbial Threats to Health, Institute of Medicine. *Emerging Infections: Microbial Threats to Health in the United States.*

Washington, DC: National Academies Press; 1992.  
[http://www.nap.edu/catalog.php?record\\_id=2008](http://www.nap.edu/catalog.php?record_id=2008)

Mason RA, Tauraso NM, Spertzel RO, Ginn RK. Yellow fever vaccine: direct challenge of monkeys given graded doses of 17D vaccine. *Appl Microbiol.* 1973 Apr;25(4):539-544.

Murphy FA. Emerging zoonoses. *Emerg Infect Dis.* 1998.  
<http://wwwnc.cdc.gov/eid/article/4/3/98-0324.htm>

Nunn CL, Hare B. Pathogen flow: what we need to know. *Am J Primatol.* 2012 Dec;74(12):1084-1087.

Pedersen AB, Davies TJ. Cross-species pathogen transmission and disease emergence in primates. *Ecohealth.* 2009 Dec;6(4):496-508.

Schaumburg F, Mugisha L, Peck B, Becker K, Gillespie TR, Peters G, Leendertz FH. Drug-resistant human *Staphylococcus aureus* in sanctuary apes pose a threat to endangered wild ape populations. *Am J Primatol.* 2012 Dec;74(12):1071-1075.

U.S. Department of Agriculture. *ARS Facilities Design Standards. Document ARS-242.1.* 2012.  
<http://www.afm.ars.usda.gov/ppweb/pdf/242-01m.pdf>

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