



Assessing Necessity of Chimpanzees in Biomedical and Behavioral Research

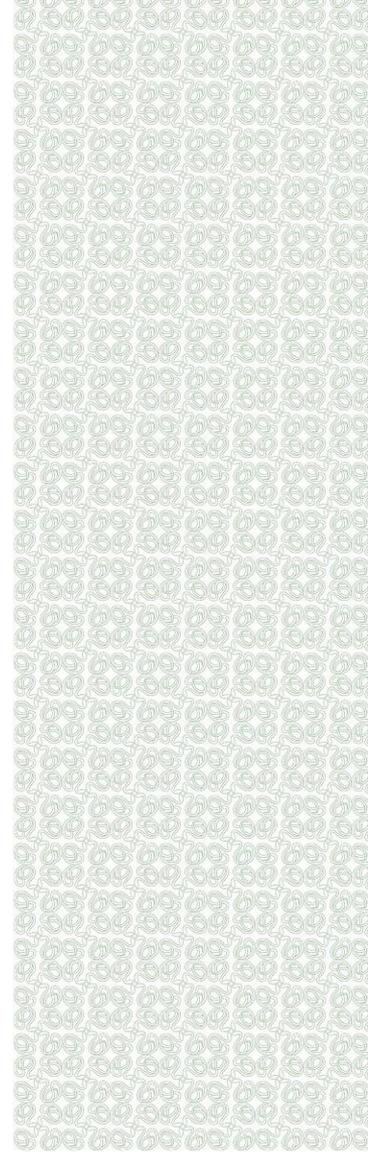
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Abbreviated Statement of Task

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, the committee will:

- 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.
- 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.

In addressing the task, the committee will explore 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.



Committee Membership

Jeffrey Kahn (Chair), Johns Hopkins Berman Institute of Bioethics

John Bartlett, Johns Hopkins University School of Medicine

H. Russell Bernard, University of Florida

Floyd Bloom, The Scripps Research Institute

Warner Greene, University of California, San Francisco

Diane Griffin, Johns Hopkins Bloomberg School of Public Health

Edward Harlow, Harvard Medical School

Jay Kaplan, Wake Forest School of Medicine

Margaret Landi, GlaxoSmithKline

Frederick Murphy, The University of Texas Medical Branch at Galveston

Robert Sapolsky, Stanford University

Sharon Terry, Genetic Alliance



Briefing Overview

- Project Timeline
- Methods
- Principles Guiding the Use of Chimpanzees in Research
- Ethical Considerations
- Biomedical Criteria & Conclusions
 - Case Studies
- Comparative Genomics and Behavioral Criteria & Conclusions
 - Case Studies
- General Conclusions
- Recommendations
- Future Use



Project Timeline



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Methods

- Three 2-day meetings, including two public information-gathering sessions. The objectives were:
 - Obtain background information on the current use of chimpanzees
 - Explore potential alternative research models to chimpanzees
 - Seek public comment about the scientific necessity for chimpanzees
- Conference calls
- Solicited public comments
 - Received 5700+ comments
- Examination of current availability and use
 - RePORTER Analysis
- Review of scientific literature
- Commissioned paper titled “Comparison of Immunity to Pathogens in Humans, Chimpanzees, and Macaques”
- Identification of a set of core principles to guide current and future use
- Development of research criteria

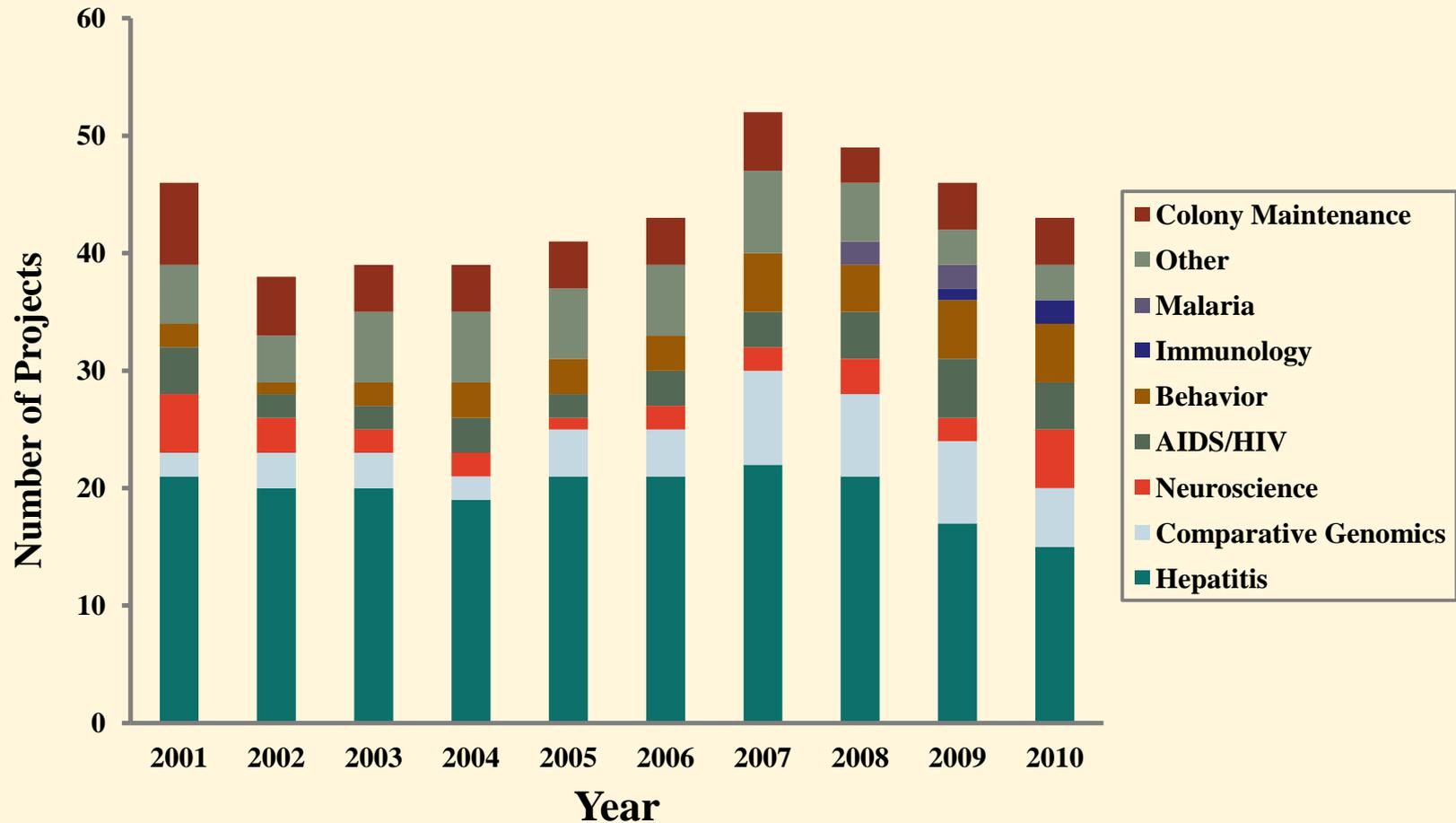


Number of Chimpanzees

	Total Number of Chimpanzees	Number of Chimpanzees supported by the NCRR, NIH
Alamogordo Primate Facility	176	176
Michale E. Keeling Center for Comparative Medicine and Research	176	159
New Iberia Research Center	347	124
Southwest National Primate Research Center	153	153
Yerkes National Primate Research Center	85	0
Total	937	612



Chimpanzee Research Supported by the NIH



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Principles

The committee was guided by the following three principles:

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 in either ethologically appropriate physical and social environments or in natural habitats.



Ethical Considerations

The committee felt ethics was at the core of any discussion about the necessity of continued use of chimpanzees in research. While the committee was not sufficiently constituted to take on the ethics of research on chimpanzees, its considerations were suffused with an awareness of the moral cost of such research. These concerns were manifest in the very high level of justification the committee required to support the necessity of chimpanzee research in the specific areas of research it examined and assessed.



Biomedical Criteria

1. There is no other suitable model available, such as *in vitro*, non-human *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.

Specific and full scientific justification for use of the chimpanzee must meet all three of the above criteria. Assessment of whether proposed uses meet these criteria should be done prospectively on a study-by-study basis. It is important that justification be substantiated including adequate supporting evidence.



Case Study: Monoclonal Antibodies

1. Development of mAbs

Criteria 1: No Suitable Alternative Models

- It is possible to develop mAb that bind to a single site in species other than chimpanzees.
 - Binding domains from other species are commonly converted into fully humanized antibodies.
- mAbs prepared in other species with properties similar to chimpanzee antibodies are already described in the literature.
- Genetic humanization of the immunoglobulin locus in mice allows for rapid and high throughput production of fully human antibodies.

Finding: Production of mAb following immunization in other species or through *in vitro* methods is equally powerful for the generation of such reagents. The continued use of chimpanzees for production of mAb does not meet the suggested criteria.



Case Study: Monoclonal Antibodies

2. Safety Testing of mAbs

Criteria 1: No Suitable Alternative Models

- The chimpanzee has been a key model for measurement of mAb safety.
 - The chimpanzee's close relationship provides information about analogous binding sites, immune responses, kinetics, and clearance.
- Chimpanzee preclinical tests may predict adverse effects.
 - Adverse events may arise due to unknown roles in the body and off-target toxicity.
- Other models, such as NHPs, have not proven as effective for detecting such toxicities.
- There are multiple methods that lessen the need for safety tests in chimpanzees.
 - Genetic engineering of the target protein in rodents
 - Selection of antibodies that recognize target epitopes shared across species
 - Selection of multiple antibodies that can serve as surrogates for responses



2. Safety Testing of mAbs (cont.)

Criteria 2: Research Cannot be Ethically Performed on Human Subjects

- Microdosing in humans may lower the dependence on safety testing in chimpanzees.
- mAb treatments which have shown good PK/PD and toxicology results in preclinical studies in other models can be tested for safety directly in humans using microdosing schedules, such as using minimal anticipated biological effect level (MABEL)

Finding: The chimpanzee is largely unnecessary in the development of future monoclonal antibody therapies due to the ongoing use of other methods (e.g. genetically engineered rodents and surrogate antibodies). There may be a limited number of mAb research projects currently in the developmental pipeline that may require the continued use of chimpanzees. These will work through the research pipeline within a few years, and the NIH should be expeditious in supporting the development of broadly accessible recombinant technologies for development of novel therapeutic mAbs to obviate the future need for chimpanzees.



Case Study: Therapeutic HCV Vaccine

Criteria 1: No Suitable Alternative Models

- Chimpanzees and humans represent the only acceptable options for testing.
 - Small animal models are in development but are not yet sufficient.

Criteria 2: Research Cannot be Ethically Performed on Human Subjects

- Therapeutic vaccine candidates can be tested in ethically acceptable research involving human subjects chronically infected with HCV.
 - Chimpanzees produce weaker neutralizing antibody responses than humans and fail to respond to interferon like most humans.

Criteria 3: Significant Impact of Forgoing Chimpanzee Use

- Testing in consenting chronically HCV-infected human subjects without prior experimentation in chimpanzees could accelerate development of a therapeutic HCV vaccine.

Finding: Chimpanzees are not necessary for development and testing of a therapeutic HCV vaccine. Use of consenting HCV-infected human subjects for testing without prior assessment of these vaccines in chimpanzees might in fact accelerate identification of an efficacious vaccine.



Case Study: Prophylactic HCV Vaccine

Criteria 1: No Suitable Alternative Models

- Chimpanzees and humans are the only two species that are susceptible to HCV infection.
- Currently no other suitable models exist for evaluation.
 - Current mouse models in development do not allow evaluation of the human protective immune response against HCV.
 - No current *in vitro* system exists that displays both HCV infectivity and the capability of an effective anti-HCV adaptive immune response

Criteria 2: Research Cannot be Ethically Performed on Human Subjects

- Studies on consenting humans at high risk for HCV infection can be ethically performed, provided these vaccines are first shown to be safe and immunogenic in experimental animals.
- One clear advantage offered by the chimpanzee model is the ability to infect the animals at a precise time following administration of a vaccine candidate (challenge experiments).



Case Study: Prophylactic HCV Vaccine (cont.)

Criteria 3: Significant Impact of Forgoing Chimpanzee Use

- While ethical studies in high-risk human populations can and ultimately must be performed, such trials are likely to prove challenging and time-consuming.
- The use of the chimpanzee could potentially speed identification of promising vaccine candidates.
- Differences in the pathogenesis of HCV infection in chimpanzees and humans must be considered in judging various vaccines.

Finding: After consideration of all these facts, the committee was evenly split and unable to reach consensus on the necessity of the chimpanzee model, and on whether or how much the model would accelerate or improve prophylactic HCV vaccine development. Specifically the committee could not reach agreement on whether a preclinical challenge study using the chimpanzee model was necessary and if or how much the chimpanzee model would accelerate or improve development of prophylactic HCV vaccines.



Biomedical Research Conclusions

While the chimpanzee has been a valuable animal model in past research, most current use of chimpanzees for biomedical research is unnecessary based on the criteria established by the committee, except for two potential current research uses:

- Development of future monoclonal antibody therapies will not require the chimpanzee, due to currently available technologies. However, there may be a limited number of monoclonal antibodies already in the developmental pipeline that may require the continued use of chimpanzees.
- The committee was evenly split and unable to reach consensus on the necessity of the chimpanzee for the development of a prophylactic HCV vaccine. Specifically the committee could not reach agreement on whether a pre-clinical challenge study using the chimpanzee model was necessary and if or how much the chimpanzee model would accelerate or improve prophylactic HCV vaccine development.



Comparative Genomics & Behavioral Research 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, in a manner that minimizes pain and distress, and is minimally invasive.

Specific and full scientific justification for the continued and future use of the chimpanzee must meet the above criteria, as well as the housing and maintenance requirements described in the report. This assessment should be applied prospectively on a study-by-study basis.

Research that relies on the use of existing samples or data would be exempt from the criteria.



Case Study: Comparative Genomics (FOXP2)

Criteria 1: Studies Provide Otherwise Unattainable Insight

- Changes in the FOXP2 gene that occurred during human evolution significantly affect gene expression in the human brain, potentially underlying the obligatory nature of human symbolic abilities and language.
- Confirm the hypothesis that the differences between chimpanzees and humans derive less from DNA sequence than from differences in gene expression and regulation.

Criteria 2: All Experiments are Performed on Acquiescent Animals and in a Manner that Minimizes Distress

- This experiment required blood samples only. The general criteria for species-appropriate housing, acquiescence to procedures, and minimal distress for manipulations were fulfilled to the extent that could be determined from information in available publications.

Finding: Given the information provided in the publication, this case example meets the committee's criteria.



Case Study: Joint Attention Cognition

Criteria 1: Studies Provide Otherwise Unattainable Insight

- Chimpanzees and humans uniquely share a high convoluted and lateralized cerebral cortex and the ability to engage in joint attention.
- Investigation into joint attention is likely to provide otherwise unattainable insight into the neurodevelopment of communication, and by implication, communicative disorders.

Criteria 2: All Experiments are Performed on Acquiescent Animals and in a Manner that Minimizes Distress

- Animals acquiesced to behavioral testing during the awake part of the procedure and were trained to present for anesthesia.

Finding: The study could potentially meet all criteria for approval if sufficient additional assurances were provided about chimpanzee housing and groupings, and the number and duration of procedures were minimized.



Comparative Genomics and Behavioral Research

Conclusions

- Comparative genomics research may be necessary for understanding human development, disease mechanisms and susceptibility, because of the genetic proximity of the chimpanzee to humans. It poses no risk to the chimpanzee when biological materials are derived from existing samples, and poses minimal risk of pain and distress in instances where samples are collected from living animals.
- Chimpanzees may be necessary for obtaining otherwise unattainable insights to support understanding of social and behavioral factors that include the development, prevention, or treatment of disease.



General Conclusions

- The chimpanzee has been a valuable animal model.
- There is no uniform set of criteria currently used to assess the necessity of the chimpanzee in NIH-funded biomedical and behavioral research.
- Application of the committee's criteria would provide a framework to assess scientific necessity to guide the future use of chimpanzees in biomedical, comparative genomics, and behavioral research.
- The present trajectory indicates a decreasing scientific need for chimpanzee studies due to the emergence of non-chimpanzee models and technologies.
- Development of non-chimpanzee models requires continued support by the NIH.



Recommendation 1:

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*, non-human *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 either be maintained in ethologically appropriate physical and social environments or in natural habitats. Biomedical research utilizing stored samples is exempt from these criteria.



Recommendation 2:

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 either be maintained in ethologically appropriate physical and social environment or in natural habitats. Comparative genomics and behavioral research utilizing stored samples are exempt from these criteria.



Future Use of Chimpanzees

Finding: The committee cannot predict or forecast future need of the chimpanzee animal model and encourages use of the criteria established when assessing the potential necessity of chimpanzees for future research uses.

Conclusion: A new, emerging, or re-emerging disease or disorder may present challenges to treatment, prevention and/or control that defy non-chimpanzee models and available technologies and therefore may require the future use of chimpanzees.



Independent Oversight Committee

- The criteria set forth in the report are intended to guide not only current research policy, but also decisions regarding potential use of the chimpanzee in future research.
- The committee acknowledges that imposing an outright and immediate prohibition of funding could cause unacceptable losses to research programs as well as have an impact on the animals.
- Therefore, the committee believes 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 that builds on the Interagency Animal Model Committee and uses the recommended criteria.



Obtain Additional Information

Study Website <http://iom.edu/chimpstudy>

Download the report

Download public meeting agendas and presentations

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Case Study: Respiratory Syncytial Virus (RSV)

Criteria 1: No Suitable Alternative Models

- Multiple non-chimpanzee models, including mice, sheep and cotton rats, exist that demonstrate susceptibility to RSV and the ability to develop clinical signs of the virus. The last paper published to use the chimpanzee was in 2000.

Criteria 2: Research Cannot be Ethically Performed on Human Subjects

- The recent development of a human challenge model suggests that RSV vaccines and antivirals can be safely tested on human subjects.

Criteria 3: Significant Impact of Forgoing Chimpanzee Use

- Eleven companies are currently in preclinical or clinical trials with RSV vaccines or antivirals.

Finding: Currently chimpanzee use for RSV research is not necessary. The committee acknowledges that there are still barriers in the development of a prophylactic RSV vaccine and therefore the necessity of chimpanzee use for future for testing of novel vaccines would need to be assessed using the committee's criteria as research is proposed.

Case Study: HCV Antiviral Drugs

Criteria 1: No Suitable Alternative Models

- There has been a steady de-emphasis of the use of chimpanzees, in part due to availability of other animal models.
- Two antivirals, boceprevir and telaprevir, were developed and approved without the use of chimpanzees.

Criteria 2: Research Cannot be Ethically Performed on Human Subjects

- Phase 0 studies of drug candidates can be performed in consenting humans, using microdosing research designs.
- Early phase toxicity or efficacy studies could be performed in consenting individuals chronically infected with HCV.

Criteria 3: Significant Impact of Forgoing Chimpanzee Use

- Many new classes of antivirals are already approved or in advanced clinical trials, which do not rely on use of chimpanzees.

Finding: Chimpanzees are not necessary for HCV antiviral drug discovery and development, and there is not foreseeable future necessity of the chimpanzee model.



Case Study: Altruism

Criteria 1: Studies Provide Otherwise Unattainable Insight

- Chimpanzees maybe particularly relevant for addressing complex behaviors because of shared evolutionary history and recent common ancestry.
- In this study, animals behaved prosocially towards their partners irrespective of relative social status, genetic relationship, or expectation of reciprocity.
- These results imply that human beings may have a tendency to help other individuals unconditionally, at least when the help can be given at no cost.

Criteria 2: All Experiments are Performed on Acquiescent Animals and in a Manner that Minimizes Distress

- Animals were temporarily removed from their usual housing and social group to engage in a cognitive task paired with other chimpanzees. This study could meet the criteria; more complete descriptions of housing and handling are necessary to make a conclusive determination in this specific example.

Finding: This study exemplifies the numerous cognitive investigations that have been done in chimpanzees. Many such studies would be similarly approvable under the recommended criteria.

