## Information Requested/Request for Comment

The NIH seeks comments on any or all, but not limited to, the following topics:

*Rigor and Transparency*

**The challenges of rigor and transparency in animal research and actions NIH can take to improve the quality of animal research including rigor and transparency.**
We agree this topic is critical and suggest that NIH issue guidelines for disclosure of animal care and procedure details in grant applications and manuscripts. NIH could recommend that all journals follow their recommendations. Details regarding water purification, chow content, enrichment, stress, handling, as well as all experimental procedures should be included. Recognition of differences in sensory abilities and species-specific differences may be highly relevant. No detail should be left unreported, including season of the year that studies were conducted in. Animal worker exposure to other animals (pets) could influence outcomes in the laboratory. This factor should also be controlled.

**How preregistration, the process of specifying the research plan in advance of the study and submitting it to a registry, would impact animal research including improving the quality of scientific research.**

**While preregistration is often considered in the context of hypothesis-testing and confirmatory experiments, would it be useful at other stages of the research process, such as the exploratory and hypothesis generating?**
Preregistration of animal studies may have some value in certain circumstances, but lack of evidence for consistently beneficial outcomes is mitigated by concern for the administrative burden involved. Methods to standardization popular animal tests, including in primates would be of utility as it could reduce variation in outcomes.

**How to address the complexity and expense related to use of large animals, including nonhuman primates, that may provide biologically more relevant models?**
We agree that large animals have great value in research and should be accommodated by NIH guidelines. Reverse translational approaches can be very valuable in the use of large animals as well as small animal studies. While expensive, nonhuman primate studies are essential to translational model. Reducing costs seem essential to the capacity to use nonhuman primates. Minimizing animal numbers becomes ever more important and all methods to address this issue should be considered, dependent on the question and experimental design. Innovation in this realm should be encouraged.

**How NIH can partner with the academic community, professional societies, and the private sector to enhance animal research quality though scientific rigor and transparency.**
Here again, greater standardization of animal research tests would be of utility.
*Optimizing the Relevance to Human Biology and Disease*

**Actions NIH can take to facilitate the translatability of animal research to human biology and disease.**
The translational/ predictive validity of behavioral tests needs be based on published research. Currently some institutes have implemented behavioral guidelines that remove the ability to use some tests that have evidence of strong predictive and translational validity from the literature. For example, the forced swim test (FST) has been demonstrated to predict every current clinical antidepressant from SSRIs to deep brain stimulation (DBS) (Garcia et al., 2008; Hamani & Nóbrega, 2010; Slattery & Cryan, 2012), while non-antidepressant drugs do not affect behavior in this task (Cryan, Markou, & Lucki, 2002). The FST was instrumental to developing novel non-monoaminergic antidepressant therapies including, ketamine and allopregnanolone (Brachman et al., 2016; Garcia et al., 2008; Melón, Hammond, Lewis, & Maguire, 2018). Allopregnanolone was highlighted as an example of how basic neuroscience can lead to novel psychiatric medications (Gordon, 2019), and that drug development relied on the FST (Melón et al., 2018). Some researchers have overinterpreted the test as being in itself a model of depression, which lead some institutes to recommend avoidance of this test. Rather than blacklisting a useful test, it would be helpful to produce guidelines for the language to use when describing the behavioral response to this test.

Another way to improve translational validity would be to encourage preclinical researchers to use human clinical data to back translate into animal models and to encourage and incentivize collaborative projects between preclinical and clinical researchers. The focus on reductionism for preclinical work has contributed to the lack of translation. For clinical studies, multidimensional measures are used to diagnose disease and determine treatment efficacy. It is understood that multiple brain regions and biological processes contribute to disease state. In preclinical work researchers are currently encouraged to focus on a specific brain circuit, region or biological process with a directly influenced behavioral endpoint because we cannot model a disease state, only symptomology. When drugs are designed to only influence one brain region and one symptom they are going to fail when multidimensional metrics are used. Taking a systems approach to drug development and creating test batteries that closely match the measurements for drug efficacy in humans will increase translatability.

**How to encourage researchers to select or develop animal models with high utility and design experiments that have external validity to the clinical populations.**
See response above.

**How NIH can partner with the academic community, professional societies, and the private sector to enhance animal research translatability.**
NIH can organize symposia in conjunction with leaders in their portfolios to highlight these issues in scientific sessions at major meetings including ACNP.

*Research Culture*

**How research culture drives the choice of animal models.**

**How incentives/disincentives in the research enterprise influence research using animal**
Science is an incredibly expensive enterprise and funds are very limited. As such, many researchers try to use the least expensive animal model possible and sometimes even leave out important controls to cut down on the cost of experiments. Increased funding for proper experimental design would be an excellent incentive.

**How all researchers, including trainees, are educated in rigorous research design, statistical considerations, transparent research practices, and the role of NIH in this training.**
There is a lot of variability in the training of statistical considerations. If NIH were willing to produce webinars on this subject it could augment the training researchers are receiving at academic institutions.

NIH should also issue guidelines for disclosure of animal care and procedure details in grant applications and manuscripts and recommend that all journals follow their recommendations. Details regarding water purification, chow, enrichment, stress, handling, as well as all experimental procedures should be included. Recognition of differences in sensory abilities across species may be highly relevant. No detail should be left unreported, including season of the year that studies were conducted, animal worker exposure to other animals (pets), animal facility noise abatement, etc.