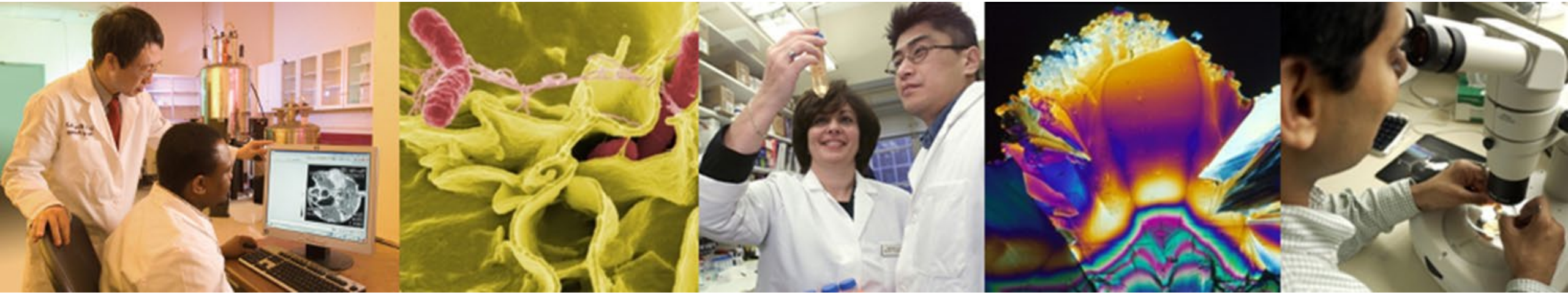
ACD Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research

Second Interim Report

121st Meeting of the Advisory Committee to the Director (ACD)

December 11, 2020



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Principal Deputy Director, NIH
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Agenda

- **Review Charge**
- Themes -> Recommendations
- Final Steps

Charge to the Working Group (October, 2019)

- **Identify gaps and opportunities** to improve the rigor, reproducibility, translational validity, and transparency of animal models studies

- Evaluate **how animal models of human disease are currently developed, validated, and accepted into routine use**, and how this process could be improved

- Consider the process for **validating alternative models** to animal research

Charge to the Working Group (October, 2019)

- Consider benefits and burdens of **registering animal studies** that aim to lead to first human trials

- Model **financial implications of potential changes in the average costs** of grants using animal models, the number of studies funded, or the need to develop consortia to achieve appropriate statistical power

- Consider how rigor in animal research is incorporated into **training**

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ACD Enhancing Rigor, Transparency, and Translatability in Animal Research Working Group **Support**

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Vocabulary and Framework

In the context of Animal Research:

- **Discovery Research:** Research to illuminate how biological systems work.
- **Preclinical Research:** Research that is needed to inform and lead to human clinical trials.
  - **Early-Stage Preclinical Research:** Animal research to understand the basis of human biology, disease or disorders and develop interventions. *This NIH usage is inclusive, and we note that industry uses the term more narrowly to mean research focused on assessing the efficacy of candidate therapeutics .*
  - **Late-Stage Preclinical Research:** Research using animals to find out if a treatment is likely to be efficacious. Often done immediately before testing in humans.
- **Translation:** Applying results from preclinical research, usually via late-stage preclinical animal studies, to justify, design and execute trials in humans.

Vocabulary and Framework

- **Rigor** - Application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation and reporting of results.
- **Reproducibility**
  - **Methods reproducibility** - Providing enough procedural detail and data to repeat successfully.
  - **Results reproducibility** - Getting the same results from a new study with procedures as close to the original as possible.
  - **Inferential reproducibility** - Drawing similar conclusions or making knowledge claims of similar strength from study replications and re-analyses.
- **Transparency** - accessibility of information

Discussion Considerations

Will it substantially improve Rigor, Transparency?

- Is it possible?
- What burdens will it add?
- What is the benefit/burden ratio?
- How does it apply to different stages and kinds of research (hypothesis generating versus hypothesis testing)?
- How can we streamline and incentivize?
- Should it be required?
- Effect across various animal systems?
- How will NIH evaluate costs and success?
- Effect on translatability to human biology or clinical trials?

Is there a transformative vision or opportunity?

Unifying Themes

- Elevate AWARENESS of rigor related expectations, problems, solutions, resources
- Provide tools and infrastructure to support best practices
- Improve rigor at the design and grant application stage
- Acquire systematic data on study design and animal use prospectively and retrospectively
  - Key data need to be computable
  - Commit to data-driven review of costs/benefits
- Balance the benefit/burden ratio of rigor tools as experiments move along the discovery continuum from discovery phase to late-stage preclincal studies
- Pilot, measure, evaluate, adjust
- Incentivize, monitor, and as needed, enforce

Statistics: Expectations, Needs and Opportunities

- Animal research needs good study design, statistical data analysis and results reporting – without them, even the best animal models are useless

- Applied statistical practices in animal research lag behind many other fields, especially clinical research
  - Animal researchers often don’t get relevant statistical training
  - Too few applied statisticians are available to consult for animal researchers
  - Many fields lack a culture of collaboration between statisticians and animal researchers
  - Problems with study design, sample size/statistical power and data analysis plans are not caught at the grant peer review stage

Statistics: Expectations, Needs and Opportunities

Transformative opportunity

- Educate researchers and community about reproducibility expectations
- Educate in best practices
  - New teaching resources
  - NIH training program requirements
- Increase pool of domain knowledgeable statisticians
- Elevate statistical design and analysis practices from grant application to final publication

Statistics: Design and Analysis

IMPROVE STUDY DESIGN AND ANALYSIS & INCREASE TRANSPARENT REPORTING

- At the study design stage in the grant application, with influence at review and funding. The proposal from the Rigor Guidelines group is one mechanism.

- Where appropriate, expect effect sizes (or other estimates from statistical analyses) for animal studies to be reported with confidence intervals and the interpretation of these estimates to be discussed within the given scientific context.

- At the review stage provide statistical expertise on grant review panels.

- At the publication stage expect all publications of NIH-funded preclinical animal research to include the ARRIVE2 Essential 10.

Care, Environment, Husbandry and Microbiome

- Factors in animal care, environment, husbandry and microbiome - once unknown or treated as irrelevant – affect biological responses and should therefore inform study design and outcome interpretation
- Standardization of all factors is impossible.
- Focus instead on raising awareness; on recording and reporting from beginning to end of research process
- Transformative new opportunities from
  - Data mining and use by researchers and by NIH
  - Generating new knowledge about variables, including the animal microbiome
  - Learning how these variables affect translation to humans

Care, Environment, Husbandry and Microbiome

Record and report extrinsic care factors From Design to Publication

- **Design expectations:** Educate investigators about potential confounding extrinsic variables from the time of study design and grant submission
- **Prospective reporting and uses:**
  - Address and/or analyze these variables in study design
  - Record key elements in Vertebrate Animal Section (VAS)
  - Data structure and AI Aspects of the key elements: Design in light of how investigators, NIH, animal research professionals need to use the data.
- **Retrospective reporting:** Require ARRIVE2 Essential 10 for all funded manuscripts to improve transparency and reproducibility.
  - Assess and optimize data structure, potential computability and potential data mining

Care, Environment, Husbandry and Microbiome

Prospective reporting: Working list of key animal factors for revised VAS

Describe the following extrinsic animal care factors for the species proposed:

☐	Caging and housing arrangement (e.g., static or ventilated, open-topped or filter-topped; size of housing space), cage components, material and opacity
☐	Cage/pen change frequency
☐	Room temperature range
☐	Room relative humidity range
☐	Air exchange rate in rooms/flow rate in rodent cage
☐	Light intensity, light color, altered light cycle
☐	Bedding substate (e.g., corncob, paper chips)
☐	Environmental complexity and enrichment type (e.g., nestlets, climbing structures, etc.)
☐	Diet (including type, source, supplements, feeding method and frequency, method of preparation, water quality, type and supply)
☐	Veterinary and supportive treatments provided
☐	Chemicals and methods used for sanitation of housing area
☐	Enclosure density (number of animals co-housed in a shared space)
☐	Vendor source/source of origin
☐	Known underlying or adverse clinical issues (e.g., dermatitis, diabetic, prone to seizures)
☐	Any additional interventions for consideration for this animal model

Adjust for species groups?

Computability?

Accessibility of these data to research community.

Relationship to retrospective Reporting.

Use cases for these data.

Care, Environment, Husbandry and Microbiome

ESTABLISH A TASK FORCE TO CATALOG AND EVALUATE THE EFFECT OF EXTRINSIC FACTORS

- Assess what factors should be cataloged
- Assess what measures of impact can and should be systematically recorded
- Identify how information should be stored, retained, and mined
- Use to guide modification of the key animal factor list to be reported
- Review and advise incentives and enforcement mechanisms to assure reporting

DEDICATE FUNDS FOR CONTROLLED RANDOMIZED TRIALS TO TEST THE EFFECT OF EXTRINSIC VARIABLES

- Extrinsic animal care factors
- The Animal Microbiome

Animal Model Development, Selection and Evaluation

- Animal models, like all models, are imperfect.
- Rigorous model design and selection can mitigate limitations.
- Design and selection should:
  - Consider the experimental intent (discovery vs. modeling therapeutic intervention)
  - Should align to a specific question or hypothesis
  - Should integrate what is known about the relevant human and animal biology
  - Should consider that biology at all levels of its complexity

Animal Model Development, Selection and Evaluation

IMPROVE DESIGN, SELECTION AND EVALUATION OF ANIMAL MODELS

- Design and selection should consider the experimental intent and the research question of interest.
- Establish a framework for rationalizing animal model selection
- Establish/identify a venue for the exchange of information and best practices
- Encourage and support expert groups to evaluate important models and recommend best practices and changes, if justified, of specific animal model
- NIH can and should assist, as needed, in implementing changes in model choice
- Support projects to establish high-value better animal models

Large and Long-Lived Species

Larger and long-lived species can provide higher fidelity predictors of translatability. In other instances, they are the only non-human system available.

Document information about long-lived animal's history

- Formalize a mechanism to record and manage individual animal-level meta data
- Be transparent and harmonize by using checklists (e.g. ARRIVE2).

Provide adequate research support

- Create policy to accommodate longer timeframes and higher budgets
- Continue to develop national resources to produce large animals

Improve community understanding and awareness of resources

- Such as the sharing of non-published data (example: Open Source for Nonhuman Primate Optogenetics) and creation of large databases (example: National NHP DNA Bank)

Animal Model Development, Selection and Evaluation

Experimental Systems: Models for, not of
Joshua A. Gordon, MD, PhD; NIMH

Animal Models in NIGMS-Funded Sepsis Research
Jon R. Lorsch, PhD; NIGMS

From Mice to Medicine Improving the Rigor, Reproducibility and Predictive Validity of Preclinical Research for Alzheimer's Disease
Lorenzo Refolo, PhD; NIA

Concept for Reproducible Animal Models for Complex Human Disease: Implications for Personalized Medicine
Catherine Kaczorowski, PhD; The Jackson Laboratory

(Move over, Mice!): PhysioMimetics: Integration of Organs-on-Chips with Systems Biology to Humanize Drug Development
Linda G. Griffith, PhD; MIT

Animal Model Development, Selection and Evaluation

CHARTER A HIGH-LEVEL WORKING GROUP ON 'NON-ANIMAL MODELING SYSTEMS IN BIOMEDICAL RESEARCH' TO ADDRESS

- How to better meet critical needs when no animal model exists
- Develop a framework and process for assessing the human relevance of non-animal models and their value in complementing or replacing existing animal models
- Maximize innovation potential
- Convene and nurture this highly interdisciplinary emerging area

Checklists and Guidelines

GOAL: ACHIEVE BETTER REPORTING AND REVIEW OF ELEMENTS OF RIGOR IN ANIMAL RESEARCH

- Our group concluded that checklists can be an effective tool, but only with assured compliance. When used, concise checklists are most effective.
- Subcommittee thinking has evolved to prefer a dedicated reviewable section within the research plan for elements of rigor
  - Add a page to current page limit for the Research Strategy to allow critical elements of study design and rigor to be directly addressed
  - Use it to sufficiently address **Inclusion/exclusion criteria, Sample-size estimation, Data analysis plan, Blinding, and Randomization.**
- Develop a repository of resources to support successful and complete reporting of critical elements of rigor.

Elements of Rigor Proposed Page

1. Inclusion/exclusion criteria: Describe the criteria that will be used for inclusion or exclusion of samples or animals during the experiments and for data used in analysis.

2. Sample-size estimation: Provide planned sample sizes for each group and how they were derived.

3. Data analysis plan: Describe plans for data analysis, including statistical methods as appropriate, designed to answer the proposed scientific questions.

4. Blinding: Describe measures planned to blind the investigators during group allocation, the conduct of the experiment and the analysis, where applicable. If none taken and blinding is not appropriate to the study design, provide justification.

5. Randomization: Describe methods planned for random allocation to comparison groups and strategies for random sample processing and collection of data where applicable. Provide rationale if a randomization scheme is not used.

Prospective Registration of Animal Studies

Purposes: Provide assurance against selective reporting and outcome switching
Track retrospective evidence of bias control

Tool: **Prospective registration** before data collection, permanently record:

study design
analysis plan
primary outcome

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Purposes: Provide added incentive for registration
Mitigate publication bias
Promote bias control at the design stage

Tool: **Registered Report** = Journal article type
before data collection, submit prospective plan for peer review
upon successful review, publication of subsequent study guaranteed
(regardless of findings)

Prospective Registration - Educate and Raise Awareness

DEVELOP AND LAUNCH A PROGRAM TO RAISE AWARENESS AND UNDERSTANDING OF PROSPECTIVE REGISTRATION.

- Different methods of prospective registration
- How they support goals of rigor and transparency
- Address misconceptions and concerns
- Identify research designs where it is most applicable

Prospective Registration - Path to use

PRIORITIZE: Identify context(s) in which prospective registration of animal studies can best be piloted to guide future adoption

- Late-stage preclinical animal trials that inform human trials.

PILOT USES Incentivize and support prospective registration for appropriate studies in (ongoing and new) funded research proposals, to generate larger evidence basis

Prospective Registration - Evaluation

NIH WILL NEED TO DEVELOP AND IMPLEMENT AN EVALUATION PROGRAM TO TEST AND MEASURE THE EFFECT OF PROSPECTIVE REGISTRATION

ESTABLISH A WORKING GROUP TO:

- Define the evidence, data types, method of collection and analysis
- Create infrastructure and program vehicle for data to be collected, and analysis outcomes
- Publish outcomes of Prospective Registration and Registered Reports Projects
- Identify and test other means of increasing transparency of study aims, design and methodology, and adequacy of statistical analysis
- Conduct cost/benefit analysis review to guide further implementation

Evaluating Costs and Outcomes

- Monetary Costs
  - Sample Size: It is expected that improving rigor by increasing power will elevate costs - how much?
  - Research Type: How do the hypothesis generating versus hypothesis testing phases of research influence costs?
  - Translational Phase: Additional costs associated with late-stage preclinical research?
- Opportunity Costs
  - How many well powered studies within a research area? Distributed how?
  - Across all vertebrate animal research?
  - Which systems will gain or lose emphasis?
  - Across all of NIH – Animal systems versus other major components

Initial Financial Analysis

- We were charged with modeling the financial implications of potential changes in the average costs of grants using animal models, the number of studies funded, or the need to develop multi-lab consortia to achieve appropriate statistical power.

- **Critical Gap in Data and Metrics:** We made progress but the data currently available are insufficient and not designed to meet this need.

Cost Considerations: An Initial Analysis

- We were fortunate to have a data set generated by F. Daniel Ramirez et al. analyzing the rigor of 3396 articles published over 10 years in 5 leading cardiovascular journals.
- Linking these articles back to the NIH grants allows an analysis of rigor and associated costs.
  - Few papers documented randomization, blinding, or sample size estimation
  - For those that reported sample size, median values for most recent grant funding were about 30% higher, but the mean and variance were less.
  - Except for sample size, we found no clear associations between higher levels of rigor and increased costs

- Ramirez FD, Motazedian P, Jung RG, Di Santo P, MacDonald ZD, Moreland R, Simard T, Clancy AA, Russo JJ, Welch VA, Wells GA, Hibbert B. Methodological Rigor in Preclinical Cardiovascular Studies: Targets to Enhance Reproducibility and Promote Research Translation. Circ Res. 2017 Jun 9;120(12):1916-1926.
- Ramirez FD. Sex Differences in Cardiac Resynchronization Therapy Device Implantations and Complications: Tough Questions, Tougher Answers. Can J Cardiol. 2020 Mar 23:S0828-282X(20)30274-9.

Cost Related Considerations - Actions

CONTINUE COST ANALYSIS

- Extract information on other potentially important variables
- Similar or more extensive analyses on other data sets of publications
- Consider studies scientists who demonstrate the highest levels of transparency and rigor to identify enterprise best-practices

ENHANCE DETAILS IN BUDGET JUSTIFICATION SECTION

SUPPORT RESEARCH ON THE RESOURCE IMPLICATIONS OF RIGOR

Further Actions: Flagship Data Generation and Analysis

Establish animal centers of excellence

- Enhance understanding of comparative biology
- Support animal model design in defined areas of human biology
- Collate data/best practices and disseminate relevant training
- Anchor animal microbiome work
- Develop resources to produce and support large animal research

Establish NIH animal rigor improvement and evaluation program

- Generate data on rigor, reproducibility and transparency
- Determine the effect of recommendations using metrics and data
  - Preregistration
  - Extrinsic factors
  - Financial and cost implication
  - Model design, selection and use

Agenda

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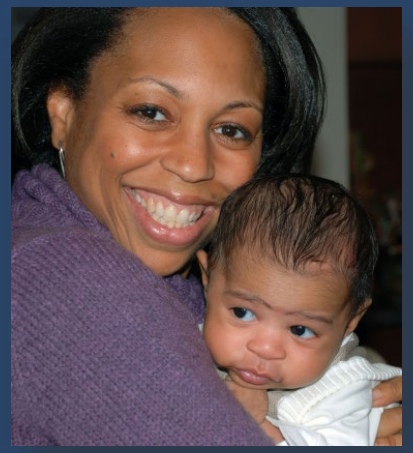
Finishing

Refine and hone recommendations

- End-user Feedback
- Data and AI perspective

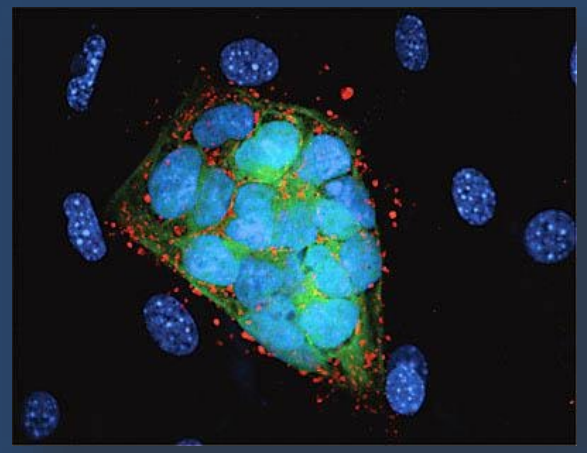
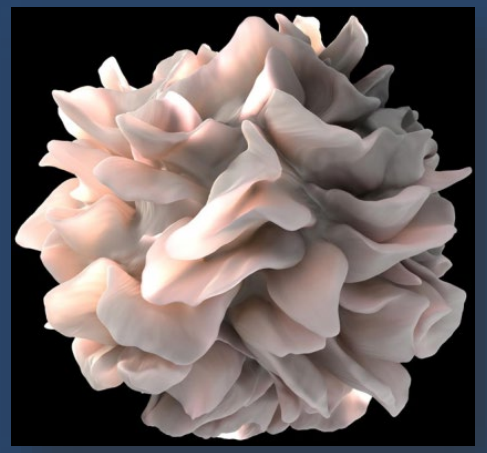
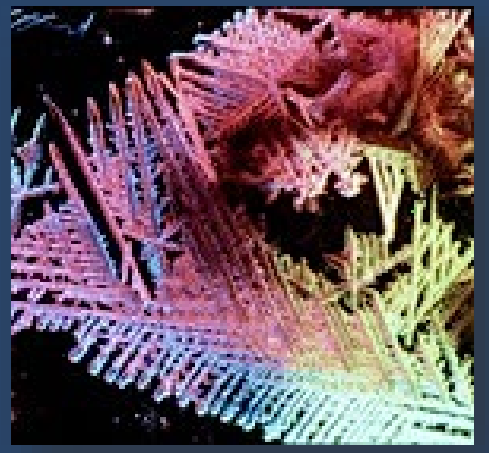
Sum the parts

- Interactions, efficiencies, anticipatable collisions




NIH…

Turning Discovery Into Health

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