Rigor and Reproducibility for the Research Administrator

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NCURA Webinar

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Outline

- Reproducibility Background
  - NIH’s initiative
  - Definition
- NIH’s Rigor and Reproducibility Requirement Overview
- Breakdown of 4 Key Areas
  - Communicating the ‘why’ and ‘how’ with researchers
  - Application instructions
  - Resources
  - Questions
- More Resources

The majority of the information in this presentation is from NIH

Participant Poll

What is your current role in research administration?
- Research Compliance and Integrity
- IRB/IACUC
- Proposal Development
- Research management/preservation
- Proposal review and submission
Don’t Be Afraid of the Science

- It is important to know where policies are coming from
- Not possible to know every detail, but knowing where to find resources is important
- Rigor and Reproducibility requirement came out two years ago, and continues to be relevant (Human Subjects and Clinical Trial policies)

Participant Poll

“Reproducibility Crisis” has been used to describe the current state of science. Based on your experience and knowledge, do you believe there is a reproducibility crisis?

- Yes
- No
- This is the first time I have heard the phrase “reproducibility crisis”
- I’ve heard “reproducibility crisis” but I don’t have an opinion on the state of science
The NIH Initiative: Enhance Research Rigor and Reproducibility

• NIH introduced initiative in October 2013 with emphasis on unbiased experiments and reproducible results\(^1\)
• January 2014 Dr. Francis Collins and Dr. Lawrence Tabak published commentary in Nature\(^2\)
• June 2014 workshop hosted by NIH with Nature publishing group and Science in attendance\(^2\)
• January 2016 NIH Rigor & Reproducibility policy takes effect

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Why a Reproducibility Initiative?

A 2012, retrospective analysis shows >50% of preclinical research results are not reproducible = ~$28 billion/year spent

Reproducibility is Not Just NIH/AHRQ

- In June 2014, NIH, Nature Publishing Group and Science discussed scientific publishing and how to enhance reproducibility
- Adopted principles and guidelines for reporting preclinical research
  - Rigorous statistical analysis
    - Journal have method to check statistical accuracy
  - Transparency in reporting
    - No limit or generous limit for methods sections
    - Require authors to fill out a checklist to state where required information is in manuscript
  - Data and material sharing
    - Require datasets be made available upon request (where appropriate)
    - Recommend sharing datasets in a public repository
  - Consideration of refutations
    - Policy stating that if journal publishes paper, assumes responsibility to consider publication of refutations of that paper
  - Considering establishing best practices
    - Image based data
    - Description of biological materials
- Endorsed by several reputable journals and professional organizations

Reproducibility Definition

“[T]he existence and propagation of one or more errors, flaws, inadequacies, or omissions (collectively referred to as errors) that prevent replication of results.”


Participant Poll
What has been challenging for your investigators when addressing Rigor and Reproducibility requirements? (check all that apply)

– Why a new policy?
– Sex as a biological variable
– Figuring out what “Scientific Premise” means
– Authentication plans (whether they are needed/how to write them)

NIH’s Rigor and Reproducibility Requirement

Four Areas to Address Scientific Rigor

Reduce bias
- Different/multiple individuals recording assessments
- Define terminology in advance
- Use independent and blinded assessors
- Etc.

Robust results
- Well-controlled experiments
- Reproducible results when repeated using the details reported in experimental design under well-controlled conditions

Area 1: Scientific premise
Area 2: Rigorous experimental design
Area 3: Relevant biological variables
Area 4: Authentication
Phase I – went into effect 1/25/16

**Rigor & Transparency**
- Impacted most RESEARCH and CAREER DEVELOPMENT grants
- To enhance reproducibility of research findings through increased scientific rigor and transparency

**What Changed**
- The application instructions for preparing the research strategy attachment.
- New "Authentication of Key Biological and/or Chemical Resources" attachment.
- Additional rigor and transparency peer review questions.

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Phase I - Progress Reports (RPPRs)

**Section B – Accomplishments**

*B.2 What was accomplished under these goals?*
- Include the approaches taken to ensure robust and unbiased results.

*B.6 What do you plan to do for the next reporting period to accomplish these goals?*
- Discuss efforts to ensure that the approach is scientifically rigorous and results are robust and unbiased.

### Special Notes and Exceptions

**Research grants excluded**
- C06, G08, G11, G12, G13, G20, R13, S06, S10, S21, SB1, U13, U55, U81, UC6, UC7, UG4, UH4, X02, and 333

**Career Development Awards excluded**
- K02, K05, and K24, as candidates for these awards are expected to have independent, peer reviewed research support at the time the career award is made.

**NOT-OD-16-012**

**Special Note on Research Resource and Related grants**
- P30, P40, P41, P2C, R24, R28, U24, U41, U42, and U2C may have slightly revised review language; please refer to the Funding Opportunity Announcement.

*R25: not subject at this time, but must read FOA carefully!


### Phase II - Formal Instruction on Rigor

- **Advance notice:** NIH & AHRQ to require formal instruction in scientific rigor and transparency to enhance reproducibility for all individuals supported by:
  - Institutional training grants: D43, T15, T32/TL1, T34, T35, T36, T37, T90/R90, and U2R
  - Institutional career development awards: K12/KL2
  - Individual fellowships: F05, F30, F31, F32, F37, F38, and FI2
How we’ve been prepping for Phase II

• Inventory of existing trainings.

• Initial discussions with the all the PIs of the institutional training grants.

• Queried PIs to know of existing courses that incorporate R&R – not many exist – still thinking through.

• Training Grant PIs/Training Grants Administrators (TGA) group

• NIGMS FOA: PAR-17-341 released 10/6/2017
  – a good place to start thinking about this……a preview of where things are going – called that out to TGA group

Advocating for Graduate Training Reform

• Reverse experimental design training – 2.34 million dollar NIH grant (GBSI, Harvard Medical School, Vanderbilt University, Purdue and MIT)

• R3 Pilot program at Johns Hopkins University
  https://hub.jhu.edu/2018/01/03/biomedical-science-education-reform-casadevall-bosch/
### Four Key Areas to Address: Research and Career Development Applications

<table>
<thead>
<tr>
<th>Key Area</th>
<th>Application Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Premise</td>
<td>Research Strategy: Significance (scored)</td>
</tr>
<tr>
<td>Scientific Rigor</td>
<td>Research Strategy: Approach (scored)</td>
</tr>
<tr>
<td>Consideration of Relevant Biological Variables, such as sex</td>
<td>Research Strategy: Approach (scored)</td>
</tr>
<tr>
<td>Authentication of Key Biological and/or Chemical Resources</td>
<td>Separate Attachment (not scored): to be saved as a single file named “Authentication of Key Resources Plan” FORMS-E, “Other Research Plan Section”:</td>
</tr>
<tr>
<td></td>
<td>*Required if project involves key biological and/or chemical resources. Recommend 1 page.</td>
</tr>
</tbody>
</table>

### Calling out the Review Criteria – Typical Research Grant

<table>
<thead>
<tr>
<th>Review Criterion</th>
<th>Proposal Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significance</strong></td>
<td>Research Strategy</td>
</tr>
<tr>
<td>Investigator</td>
<td>Biosketch</td>
</tr>
<tr>
<td>Innovation</td>
<td>Research Strategy</td>
</tr>
<tr>
<td><strong>Approach</strong></td>
<td>Research Strategy</td>
</tr>
<tr>
<td>Environment</td>
<td>Facilities and Other Resources</td>
</tr>
</tbody>
</table>
Page Limits

- With all these R&R requirements, the page limits stayed the same.

- BUT, things are starting to shift around with the new NIH HS/CT Policies.

- Watch out for page limitations (or, the circumvention of page limitations):

- Note that the application instructions in specific Funding Opportunity Announcement (FOA) *supersede* the SF 424 Application Instructions, in case there are conflicts.

- Note: K-awards **Candidate Information and Goals for Career Development and Research Strategy:** 12 pages

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For Each of the 4 Areas...

- **Scientific Rationale**
- **The Application Instructions**
- **The Review Criteria**
- **How do I write about it?**
NIH’s Rigor and Reproducibility Requirement

Four Areas to Address Scientific Rigor

- Reduce bias
  - Different/multiple individuals recording assessments
  - Define terminology in advance
  - Use independent and blinded assessors
  - Etc.

- Robust results
  - Well-controlled experiments
  - Reproducible results when repeated using the details reported in experimental design under well-controlled conditions

Area 1: Scientific premise

Area 2: Rigorous experimental design

Area 3: Relevant biological variables

Area 4: Authentication

Area 1: Why the NIH is Addressing Scientific Premise?

- Used to form the basis for the proposed research question
- Often times, cited literature demonstrates the feasibility of the proposed experimental approach (positive)
  - Wasted resources
  - Incorrect conclusions
  - Unnecessary risks for trial subjects/unjustifiable clinical trials
- Researchers are missing the “whole picture” when they fail to seek or acknowledge literature that both negates and/or confirms a proposed study

https://nexus.od.nih.gov/all/2016/01/28/scientific-premise-in-nih-grant-applications/
### Area 1: Communicating Scientific Premise

<table>
<thead>
<tr>
<th>Significance</th>
<th>Scientific Premise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective analysis</td>
<td>Retrospective consideration</td>
</tr>
</tbody>
</table>

- **Describe strengths and weaknesses** of prior research
- **Assessment of the rigor** applied to previous experimental designs (including own research—published or unpublished)
  - Identify and acknowledge shortcomings in rigor, or reporting on rigor and include plans to address issues in future
  - **Shortcomings** could include:
    - No or insufficient authentication of key resources
    - Not considering relevant biological variables
- **Exploratory grant applications** (with limited preliminary data) should include a critical assessment of the literature that either supports or contradicts research question

[Link to FAQ](https://grants.nih.gov/reproducibility/faq.html#4825)

### Area 1: Scientific Premise

**Application Instructions**

**Research Strategy – Significance:**

- “Describe the scientific premise for the proposed project, including consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application.”

Area 1: Scientific Premise
Reviewer Criteria

Latest 11/18/16:

- “The applicant should discuss the strengths and weaknesses of the prior research used to support the application and describe how the proposed research will address weaknesses or gaps identified by the applicant.

- For example, a discussion of scientific premise might include attention to the rigor of previous experimental designs, either conducted by the applicant or reported in the literature.

- A weak scientific premise, or the failure to address scientific premise adequately, may affect criterion and overall impact scores.

- The page limit is not an acceptable excuse for an applicant to not address scientific premise.”

Area 1: Scientific Premise
How do I write about it?*

Might consider clear headers and sub headers. Be consistent throughout application in formatting:

SIGNIFICANCE
Scientific Premise:
Strengths and Weaknesses of Published Research/Preliminary Data:

“These past studies have focused largely on ____________”
“However, we’re looking more closely at _______________”
“We found some conflicting results in our analysis of the past literature ________”

The New NIH HS/CT Form

• Effective for proposals due on or after 1/25/18.

• Another way to promote rigor and transparency for clinical trials.

• Complex form, requiring details on the interventions, statistical power and design, study timeline, outcome measures, etc.

I used to include some of these things in my Research Strategy. Quotes from Open Mike*

• Use the Research Strategy section to discuss the overall strategy, methodology, and analyses of your proposed research, but do not duplicate information collected in the PHS Human Subjects and Clinical Trials Information form.

• The PHS Human Subjects and Clinical Trials Information form will capture detailed study information, including eligibility criteria; inclusion of women, minorities, and children; protection and monitoring plans; and statistical design and power.

• You are encouraged to refer to information in the PHS Human Subjects and Clinical Trials Information form as appropriate in your discussion of the Research Strategy.

• Use your Specific Aims and Research Strategy attachments on the Research Plan form to tell your story and the PHS Human Subjects and Clinical Trials Information form to provide supporting details for your story. Moving study details to the new form frees up valuable space in your page-limited research plan – use it wisely!

Did I just save some pages in my Research Strategy?

• Maybe.......how about focusing more on the scientific premise?

• If the Research Strategy is about telling your story, it’s about backing up, with a really strong literature review, why you designed your proposed study in a particular way.

  – The WHY’s vs HOW’s

Questions on Area 1: Scientific Premise?

Next:
Area 2: Rigorous Experimental Design
Area 2: Why the NIH is Addressing Rigorous Experimental Design?


Area 2: Communicating Rigorous Experimental Design

- **Full transparency** of experimental details are expected in grant applications
  - Reviewers need to know all details to assess the rigor
  - Researchers (should) already be writing transparently in publications
  - Reporting checklists can help guide researchers on level of transparency
- Experimental design is discipline and project specific
- Robust approach might include descriptions of:
  - Use of standards
  - Sample size estimation
  - Randomization
  - Blinding
  - Appropriate replicates
  - Controlling for inter-operator variability
  - Statistical methods planned
  - Inclusion and exclusion criteria
  - Subject retention and attrition
  - How missing data will be handled
  - Any other information as appropriate to the science

**Transparency and consideration on how to avoid inherent bias is key!**

https://grants.nih.gov/reproducibility/index.htm
https://nexus.od.nih.gov/all/2016/01/28/scientific-rigor-in-nih-grant-applications/
Explaining “Transparency”

- Include enough detail that the reviewer can assess the rigor
  - What detail would they include in a publication?
- Reporting checklists
  - “A call for transparent reporting to optimize the predictive value of preclinical research”
    - [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3511845/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3511845/)
  - Questionnaire from Penelope:
    - [https://www.penelope.ai/equator-wizard](https://www.penelope.ai/equator-wizard)
  - EQUATOR Network:
    - [https://www.equator-network.org/library/](https://www.equator-network.org/library/)

Explaining How to Rigorously Design an Experiment

- Challenge and try
to disprove the
hypothesis
- Replication
- Validation
- Generalization
- Perturbation
- Consistency
- Power calculation
- Other statistical
considerations
- Size of observed
effect
- Consideration of
introduction
of errors
- Sensitivity analysis
- Acknowledgement of data that do not meet hypotheses
- Acknowledgement of others’ work
- Corroborate with others
Area 2: Communicating Rigorous Experimental Design

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https://nexus.od.nih.gov/all/2016/01/28/scientific-rigor-in-nih-grant-applications/

Why NIH is calling out statistics?

NIH Calling Out Statistics

- Statistics not always part of undergraduate/graduate curriculum, but used regularly to analyze data
- Inappropriate use of statistical analyses and/or inadequate number samples
  - Misleading results
  - Irreproducibility


Nuzzo. R STATISTICAL ERRORS. Nature 2014:506(7507):52. doi: 10.1038/506150a
How to “Fix” Statistics?

Five ways to fix statistics

As debate rumbles on about how and how much poor statistics is to blame for poor reproducibility, Nature asked influential statisticians to recommend one change to improve science. The common theme? The problem is not our maths, but ourselves.

Leek JM, Blakeley B., Gelman, Andrew; Colquhoun, David; Nuijten, Michele B.; Goodman, Steven N. Five ways to fix statistics. Nature 2017;551(7682):557–+

• Free statistical consulting and tutorials:
  – Center of Open Science: https://cos.io/our-services/training-services/
  – Simply Stats: https://simplystatistics.org/courses/
  – R Tutorial: http://www.r-tutor.com/

• Your institution may have statistical consulting services!

Area 2: Rigor
Application Instructions

Research Strategy – Approach – some quotes

• Describe the experimental design and methods proposed and how they will achieve robust and unbiased results.

• For trials that randomize groups or deliver interventions to groups, describe how your methods for analysis and sample size are appropriate for your plans for participant assignment and intervention delivery.

Area 2: Rigor
Review Criteria

• The applicant should describe experimental controls, plans to reduce bias (blinding, randomization, subject inclusions and exclusion criteria, etc.), power analyses, and statistical methods, as appropriate.

• [Link to Reviewer Guidelines on Rigor and Transparency]

  – NEW HS/CT Form, Sec 4.4 – Statistical Design and Power – from application instructions “Specify the number of subjects you expect to enroll, the expected effect size, the power, and the statistical methods you will use with respect to each outcome measure you listed in 4.3 Outcome Measures.” – not duplicative!

Why?

Area 2: Rigor
More on Review Criteria

• Reviewers will assess scientific rigor as part of the Approach criterion for research grant applications and the Research Plan criterion for mentored career development award applications, as well as the overall impact score.

  – The Vertebrate Animal Section no longer requires a justification of animal numbers (NOT-OD-16-006). Inadequate vertebrate animal numbers should be reflected in the score and will not result in a block to funding.

  – Reviewers will assess information concerning numbers of animals according to the section where it is included in the application.

How?
Area 2: How much detail should I include in my application regarding rigor?

- Comes from NIH FAQ, Section III: Scientific Rigor, FAQ#6
- Every detail is not expected.
- State succinctly what is planned.
  - For example: "10 males and 10 females will be randomized to blinded treatment and control groups, giving 80% power to detect a treatment effect size of 65% compared to a baseline response of 5% at a significance level of 0.05."
- Investigators should be aware of the guidelines for publishing preclinical research in journals, which are similar in intent to the new application instructions.


Area 2: Rigor
See NIH Examples in Awarded Applications (Biomedical/Lab examples)

- NIH provided four examples (next slide)
- Selected based on high overall impact scores and positive reviewer comments specific to rigor.
- Show how elements of rigor and transparency have been succinctly provided in applications.
- May not represent all of the aspects and may still have room for improvement, recognizing that many things go into the full review of applications.

Area 2: Rigor

How do I write about it? (NIH Example)

APPROACH

Scientific Rigor:

“Aim 3: Male and female mice will be randomly allocated to experimental groups at age 3 months. At this age the accumulation of CUG repeat RNA, sequestration of MBNL1, splicing defects, and myotonia are fully developed. The compound will be administered at 3 doses (25%, 50%, and 100% of the MTD) for 4 weeks, compared to vehicle-treated controls. IP administration will be used unless biodistribution studies indicate a clear preference for the IV route. A group size of n = 10 (5 males, 5 females) will provide 90% power to detect a 22% reduction of the CUG repeat RNA in quadriceps muscle by qRT-PCR (ANOVA, α set at 0.05). The treatment assignment will be blinded to investigators who participate in drug administration and endpoint analyses. This laboratory has previous experience with randomized allocation and blinded analysis using this mouse model [refs]. Their results showed good reproducibility when replicated by investigators in the pharmaceutical industry [ref].

Next:

Questions on Area 2: Experimental Rigorous Design?

Area 3: Relevant Biological Variables
Area 3: Communicating Relevant Biological Variables

- Choice of animal model or human population to be included will vary with the scientific topic of the proposed research
- Relevant biological variables (such as sex) are to be considered in research design, analyses and studies for vertebrate animals and humans
- Biological variables that may affect the outcome should be considered
  - Sex
  - Life stage
  - Weight
  - Underlying health conditions
- Applies to basic, preclinical, and clinical research
- It is expected that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies

Why the NIH is calling out sex?

Sex as a Biological Variable (SABV) Background

- Preclinical research historically has focused mainly on male animals\(^1\)
- The results of mostly single-sex studies contribute to ambiguous information on how sex-based differences may influence outcome\(^2\)
- There is increasing evidence of sex-based differences in basic genetics, cellular and biochemical organization\(^1,2\)
- Exclusion of females from preclinical studies has led to treatments with adverse events that are more common or severe in women than men\(^3\)


Strategies for Considering SABV in Research Strategy

Considering SABV is **NOT** the same as looking for differences based on sex

- Expand literature search terms: sex, gender, male/female, etc.
- Formulation of research questions
- Consider the influence of sex in study design
- Include males and females into studies or provide justification for a one sex study
- Stratified randomization of males and females into experimental conditions
- Collect/analyze sex-based data, even if study is not powered to detect sex differences
  - Examine the treatment or toxicity effects for each sex separately
  - Consider influence of sex in the interpretation of study results
- Rationale for number of study subjects now to be explained in Research Strategy

Do I Need More Animals/Human Subjects?!

- At a minimum, develop a data analysis plan that provides for the collection of data disaggregated by sex
- Investigators may need larger sample sizes, especially if expecting sex to influence the results
  - In general, studies have preliminary data/hypothesis that hint that the results may be influenced by sex
  - Differentiate sex effects: **MAY** require larger numbers of animals, or equal numbers of both sexes to ensure adequate statistical power

Strategies for Reporting SABV

**Reporting of Results**
- Report the sexes of animals
- Characterize and report study results separately for males and females
- Generalize research findings, when appropriate
- Avoid using terms like: better, improved or worse when describing sex differences

**Reporting one Sex**
- Provide justification from the scientific literature, preliminary data, or other relevant considerations
- Without strong justification, it is **expected** that both males and females will be included in research

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Janine Austin Clayton. Studying both sexes: a guiding principle for biomedicine FASEB / February 2016 30:519-524

Brian J. Prendergast, Kenneth G. Onishi, Irving Zucker. Female mice liberated for inclusion in neuroscience and biomedical research, Neuroscience & Biobehavioral Reviews, Volume 40, March 2014, Pages 1-5,
What About Cell Lines?

• Sex should be considered when using cells or tissues taken DIRECTLY from the animal or human
• Consider the possible role of sex in research
• Established cell lines:
  – NIH recognizes the difficulty in determining sex
  – Continuing to work on enhancing strategies and techniques to address challenges
  – “At this time, cell lines are not explicitly covered by this policy BUT NIH encourages investigators to consider SABV and be transparent in reporting of cells (when known) and relevant sex-specific data”

SABV Considerations and Animal Research

• Justification of species for the proposed research in vertebrate animals section
• Report on the characteristics of the research animal’s environment\(^1,2\)
  – E.g. temperature, group housing, etc.
• Clearly describe study population and do not generalize findings (ex: adult animals vs. young/juvenile adults and aged adults)\(^1\)
• Non-human primates are considered a scarce resource\(^3\)
• IACUC is not required by federal regulations to request justification of the choice of sex(es) proposed in studies, but may ask for justification in studies with only one sex\(^4\)

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1. Janine Austin Clayton. Studying both sexes: a guiding principle for biomedicine FASEB / February 2016: 30:519-524
SABV FAQs

Higher prevalence in one sex?
- Acceptable justifications may include the study of sex-specific conditions or phenomena, or investigation in which the study of one sex is scientifically appropriate.

Small sample/population availability?
- Scarce resources may be considered adequate justification based on evidence of scarcity.

Secondary Analysis? (such as a dataset i.e. Clinical Data Warehouse)?
- Be aware the limitations in the data available which thereby influence the types of questions that can be asked along with the generalizability of the research.
- Limitations in existing clinical data sets, grantees should provide strong justification including evidence of the scarcity of this type of data.

Consider relevant biological variables when possible.

https://grants.nih.gov/reproducibility/faqs.htm

Advocating for Inclusion of Sex and Gender

- Gendered Innovations at Stanford:
  [http://genderedinnovations.stanford.edu/what-is-gendered-innovations.html](http://genderedinnovations.stanford.edu/what-is-gendered-innovations.html)
- Checklists, case studies, methods to incorporate both sex and gender.
Area 3: Application Instructions: Also in Approach
Consideration of Sex and Other Relevant Biological Variables

- Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans.

- For example, strong justification from the scientific literature, preliminary data, or other relevant considerations, must be provided for applications proposing to study only one sex. Refer to the NIH Guide Notice on Sex as a Biological Variable in NIH-funded Research for additional information.

https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general/g.400-phs-398-research-plan-form.html#3

Area 3: Review Criteria

- Consideration of SABV does not necessarily mean sex differences research. See Figure 1 in “Studying both sexes = A guiding principle for biomedicine” for further detail.

- A justification is expected if the application proposes to study one sex, for example in the case of a sex-specific condition or phenomenon (e.g., ovarian or prostate cancer), acutely scare resources, or sex-specific hypotheses when there are known differences between males and females.

- Cost and absence of known sex differences are inadequate justifications for not studying both sexes.
Area 3: How do I write about it?

- Refer to Slide #50!

- Can pull ideas from here, and just explain it.

- Can be an expansion of your rigor description.

- Demonstrate you have reviewed literature that supports how you considered sex and/or other biological variables in the design of your study.
The Reduced Criteria for Vertebrate Animals Section (VAS)

- A description of veterinary care is no longer required
- Justification for the number of animals has been eliminated
- A description and justification of the method of euthanasia is required only if the method is not consistent with AVMA Guidelines for the Euthanasia of Animals

See VAS Worksheet and Checklist: [http://grants.nih.gov/grants/olaw/vertebrate_animal_section.htm](http://grants.nih.gov/grants/olaw/vertebrate_animal_section.htm)

VAS: Only state the sex of the animals

Research Strategy (Approach): must address how sex is factored into the research design

VAS: only state total # of animals proposed

Research Strategy (Approach): justification on # of animals is an element of rigor

More on VAS

Typically, all of the required elements for the VAS can be addressed within 1-2 pages. The VAS must not be used to circumvent page limits.

- Source: [https://grants.nih.gov/grants/olaw/vertebrate_animal_section.htm](https://grants.nih.gov/grants/olaw/vertebrate_animal_section.htm)
Questions on Area 3: Relevant Biological Variables?

Next:
Area 4: Authentication of Key Resources

Area 4: Why the NIH is Addressing Authentication of Key Resources?
Sometimes irreproducible results are due to inaccurate reporting of resources used

Area 4: Communicating a “Key Resource”

• Investigator determines what is a “key resource”
• Describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies, including frequency of authentication
• What is a key resource?
  – May differ from laboratory to laboratory, over time
  – May have qualities or qualification that could influence results
  – Integral to the proposed research
  – Includes resources not generated by NIH funds
  – Ex: specialty chemicals, cell lines, antibodies, other biologics, etc
  – Standard laboratory reagents that are not expected to vary do not need to be included in the plan.
    Ex: buffers, common chemical or biological reagents

Why the NIH is calling out cell lines and antibodies?

https://grants.nih.gov/reproducibility/faq.html#4846
NIH Calling Out Antibodies

• Frequently used tool but can vary: batch-to-batch, non-specific binding
  – 2011 analysis found ~25% of 246 antibodies used in epigenetic studies bound to more than one target! **FALSE POSITIVES**

• Use a trusted manufacturer
  – But STILL authenticate them!

• Resources:
  – Antybuddy https://www.ntybuddy.com/

Baker M. BLAME IT ON THE ANTIBODIES. Nature 2015;521(7552):274-76. doi: 10.1038/s11776

NIH Calling Out Cell Lines

• Subject to many potential issues
  – ~15-35% of cell lines are contaminated by Mycoplasma
  – Contamination w/ other cells: 2003 study of 550 cells leukemia-lymphoma showed ~15% contaminated

• Obtain cell lines from a trusted vendor, use a fresh cell line before starting a series of experiments - https://www.gbsi.org/about/initiatives/cell-line-authentication/

• Check to see if cell line has been reported as contaminated: http://iclac.org/databases/cross-contaminations/

• Authentication plan resources:
  – GBSI Training: https://www.gbsi.org/training/
  – ICLAC offers case studies, checklists, databases: http://iclac.org/

NIH Provides Some Authentication Plan Guidance

- Cell line authentication might include short tandem repeat (STR) profiling and mycoplasma testing
- Chemical authentication might include liquid or gas chromatography, or mass spec, NMR, etc.
- Genetically modified animals or cells might include PCR amplification or Southern blot to confirm genome modification


Authentication Plan FAQs

Key resources purchased or obtained from outside source?
- It is expected to include a plan to independently verify the identity and activity of product before use
- If product is used long-term, consider the stability of the product and how validity of the product will be assessed over time
- Data sets and databases are not a “key resource” (see below)

An outside party is performing analyses? (Centers, LabCorp, etc.)
- If they’re using a “key resource,” may request information of authentication and include within own authentication plan

Proposing to establish a new resource?
- Research conducted for resource development, including plans for validating the resource, should be described in Research Strategy section

Secondary analysis of data collected through means of a “key resource?”
- NO- data sets, databases, machinery, or electronics are not a “key resource”

[https://grants.nih.gov/reproducibility/faqs.htm](https://grants.nih.gov/reproducibility/faqs.htm)
Authentication Plan FAQs

Primary cell cultures?
– Proposing to collect primary cells for short-term culture as part of research, the activities (including plans for authentication identity of cells) should be described in Research Strategy
– If obtained from another laboratory, an authentication plan should be provided

Collecting biologics as part of research?
– One-time analysis/sample? Do not need authentication plan
– Storing samples for repeated use/using stored samples? Authentication plan needed

Imaging a key part of research?
– Using a “key resource” as part of imaging process? Authentication plan needed
– Otherwise, the parameters to ensure reproducibility of imaging needs to be addressed as part of rigorous experimental design in Research Strategy

Area 4: Resource Authentication:

The Attachment

• “If applicable to the proposed science, briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. A maximum of one page is suggested.”
  – https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general/g.400-phs-398-research-plan-form.htm#11

• Key biological and/or chemical resources may or may not be generated with NIH funds and: 1) may differ from laboratory to laboratory or over time; 2) may have qualities and/or qualifications that could influence the research data; and 3) are integral to the proposed research. These include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics.

• Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.

Area 4: Resource Authentication:
The Attachment

- Information in this section must focus only on authentication and/or validation of key resources to be used in the study as described above.

- All other methods and any data must be included within the page limits of the research strategy.

- Applications identified as non-compliant with this limitation will be withdrawn from the review process


Area 4: Reviewer Criteria

- Applicants should provide a brief plan (one page or less).
- The plan should not include authentication data.
- The plan may reflect existing guidelines or standards for authentication of a resource when such standards exist.
- Reviewers will discuss the authentication plan after scoring; comments on key resource authentication should not affect scores.
- Reviewers will comment in their written critiques and discussion at the meeting on the adequacy of the plan for key resource authentication; comments can be addressed by the applicant prior to award for meritorious applications.
- Reviewers should note if the authentication plan is missing from the application.

Area 4: Reviewer Criteria continued

• Review of this attachment will occur after scoring; comments on key resource authentication **should not affect scores**. Reviewers will comment on the **adequacy** of the plan for key resource authentication; comments can be addressed by the applicant prior to award for meritorious applications.

• After scoring of the application is complete, Scientific Review Groups (SRGs) will comment on the plans for resource authentication in a manner consistent with the scientific goals of the research. Any concerns raised about the adequacy of the plans for resource authentication should be resolved by the program official before the application/proposal is funded.

• Best practices will emerge from continued discussion and deliberation on this topic.

Questions on Area 4: Authentication of Key Resources?

**Next:**
Resources
Videos

Training video meant for NIH staff (33 minutes):
https://grants.nih.gov/reproducibility/module_1/presentation.html

NIGMS and nine other ICs issued an R25 RFA for educational activities focused on developing the skills of graduate students, postdoctoral fellows and beginning investigators with respect to conducting reproducible research.

The training products resulting from those grants will be housed at the “Clearinghouse for Training Modules to Enhance Data Reproducibility”

Encourage Faculty to Participate in Peer Review

- https://grants.nih.gov/grants/peer/becoming_peer_reviewer.htm
- Contact: ReviewerVolunteer@mail.nih.gov
- Send a brief description of your area of expertise in the body of the email (1-2 sentences) and a copy of your biosketch as an attachment.
• Resources are collected from NIH and literature
Adopting the ReaDI Program

- Resources are applicable to many researchers at most institutions
- Columbia University has created a version of the ReaDI Program that can be linked to from your institutional webpages
  - For more information contact Michelle Benson at mb3852@columbia.edu
• Details broader impact of irreproducibility in preclinical/clinical studies

Thank You

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