Rigor and Transparency in Research

To support the **highest quality science, public accountability, and social responsibility in the conduct of science**, NIH’s Rigor and Transparency efforts are intended to clarify expectations and highlight attention to four areas that may need more explicit attention by applicants and reviewers:

• Scientific premise
• Scientific rigor
• Consideration of relevant biological variables, such as sex
• Authentication of key biological and/or chemical resources

**Role of reviewers:** Assess the scientific merit of each application according to the review criteria, which include consideration of scientific premise, rigor, and consideration of relevant biological variables, and the adequacy of the authentication of key biological and/or chemical resources as an administrative issue. Evaluations should be based on current best practices in the field.
### Reviewing Rigor and Transparency of Research: RPG Applications

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<th>Applies to which applications?</th>
<th>Where will I find it in the application?</th>
<th>Where do I include it in my critique?</th>
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<td><strong>Scientific Premise</strong></td>
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<td>Research Strategy (Significance)</td>
<td>Significance</td>
<td>Is there a strong scientific premise for the project?</td>
<td>Yes</td>
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<td><strong>Scientific Rigor</strong></td>
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<td>Research Strategy (Approach)</td>
<td>Approach</td>
<td>Are there strategies to ensure a robust and unbiased approach?</td>
<td>Yes</td>
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<td><strong>Consideration of Relevant Biological Variables, Such as Sex</strong></td>
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<td>Research Strategy (Approach)</td>
<td>Approach</td>
<td>Are adequate plans to address relevant biological variables, such as sex, included for studies in vertebrate animals or human subjects?</td>
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<td><strong>Authentication of Key Biological and/or Chemical Resources</strong></td>
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<td>Comment on plans for identifying and ensuring validity of resources.</td>
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Scientific Premise: Guidance for Reviewers

GOAL: Ensure that the underlying scientific foundation of the project—concepts, previous work, and data (when relevant)—is sound.

• Pertains to the underlying evidence/data for the project
• Address under Significance (R applications) or Research plan (Ks)
• Addition to the review criteria: “Is there a strong scientific premise?”
• Specifically, has the applicant:
  ▫ Provided sufficient justification for the proposed work?
  ▫ Cited appropriate work and/or preliminary data?
  ▫ Appropriately identified strengths and weaknesses in prior work in the field?
  ▫ Proposed to fill a significant gap in the field?
  ▫ OR has the applicant explained why this is not possible?
Scientific Rigor: Guidance for Reviewers

**GOAL:** Ensure a strict application of scientific method that supports robust and unbiased design, analysis, interpretation, and reporting of results, and sufficient information for the study to be assessed and reproduced. Give careful consideration to the methods and issues that matter in your field.

- Pertains to the **proposed research**
- Address under **Approach** (R applications) or **Research Plan** (Ks)
- Addition to review criteria: Are there “strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?”
- Possible considerations, if appropriate for the scientific field and research question, include plans for:
  - determining group sizes
  - analyzing anticipated results
  - reducing bias
  - ensuring independent and blinded measurements
  - improving precision and reducing variability
  - including or excluding research subjects
  - managing missing data
Relevant Biological Variables: Guidance for Reviewers

**GOAL:** Ensure that the research accounts for sex and other relevant biological variables in developing research questions and study designs. The ways in which sex and other biological variables need to be accounted for will differ across research questions and fields of study.

- Pertains to the **proposed research**
- Applies to studies in vertebrate animals and/or human subjects
- Address in **Approach** (R applications) or **Research Plan** (Ks)
- Addition to review criteria: Are there “adequate plans to address relevant biological variables for studies in vertebrate animals or human subjects?”
- Consideration of sex is required in all studies involving human subjects or vertebrate animals (see next slide).
- Specific considerations to assess include:
  - Applies broadly to all biological variables relevant to the research such as sex, age, source, weight, or genetic strain.
  - Has the applicant considered biological variables, such as sex, that are relevant to the experimental design?
  - Will relevant biological variables be controlled or factored into the study design appropriately?
Consideration of sex, included under the umbrella of “Relevant Biological Variables”, is required in all studies involving human subjects or vertebrate animals.

NIH expectations for applicants:
- If little is known about sex differences, the application should include both sexes.
  - Sufficient numbers should be provided to inform the presence or absence of sex differences. Statistically powered comparisons between sexes may not be warranted.
  - Specific hypotheses about sex differences may not be possible.
  - Findings should be reported separately by sex in progress reports and publications.
- If sex differences are known not to exist, a strong justification should be provided if the application proposes to study one sex.
- If sex differences are known, experiments should be designed with appropriate group sizes to detect sex differences.

NIH expectations for reviewers:
- As part of the Consideration of Relevant Biological Variables, assess whether the plans to address sex as a biological variable are adequate (for studies in vertebrate animals or human subjects).
- If the study involves only one sex, is this justified scientifically?
- Assess within the context of the research question and current scientific knowledge.
Reviewer Guidance to Evaluate Sex as a Biological Variable (SABV)

Are Humans or Vertebrate Animals involved? NO

Have the PIs appropriately considered SABV in their research design/data analysis?
Accounting for SABV could be reflected in one or more of the following:
• Relevant review of available literature on influence of biological sex
• Formulation of research questions
• Incorporating both males and females into studies
• Strong justification for single-sex study
• Consideration of influence of sex in study design
• Stratified randomization of males and females into experimental conditions
• Characterization of study results for males and females
• Examination of treatment or toxicity effects for each sex differently
• Consideration of the influence of sex in the interpretation of study results
• Appropriate generalization of research findings

Within the context of the research question, could SABV be relevant to the outcome or impact of the proposed studies?

Within the context of the research question, other biological variables may be relevant and their consideration in the research design should be evaluated and factored into scoring as appropriate.

Acknowledging the goal of the application to test for sex differences?

Acknowledging the design/analysis is adequately rigorous to test for sex differences?

Note: Within the context of the research question, other biological variables may be relevant and their consideration in the research design should be evaluated and factored into scoring as appropriate.
Plan for Resource Authentication: Guidance for Reviewers

GOAL: Ensure processes are in place to identify and regularly validate key resources used in their research and avoid unreliable research as a result of misidentified or contaminated resources.

- Researchers are expected to authenticate key biological and/or chemical resources used in their research, to ensure that the resources are genuine.
- New Additional Review Consideration
  - Authentication of Key Biological and/or Chemical Resources: For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.
- Rate as acceptable/unacceptable (provide brief explanation if unacceptable)
- Does not affect criterion scores or overall impact score
RIGOR AND TRANSPARENCY – UPDATE

So How Did It Go? Overall, reviewers rose to the challenge.
Since our June, 2016 meeting we have been implementing the rigor and transparency policy. We have conducted several conference calls and provided reviewers with instruction materials in an attempt to make clear the NIH expectations that changes were needed in the wording and substance of reviews. NIH asked reviewers to consider four new emphases:

- Scientific premise
- Scientific rigor
- Consideration of relevant biological variables, including sex
- Authentication of key biological and/or chemical resources

Most reviewers made explicit notes on these factors in their critiques, and the topics came up in panel discussions. But work remains. Not everyone got the message. NIH continues efforts to make it clear that it has elevated the degree of attention that must be paid to sex as a biological variable, and also to resource authentication. Even those reviewers who have always thought carefully about scientific premise and rigor should reflect on the design and methodological considerations that are critical for work in their field. Some reviewers thought about the new emphases but used old language in their critiques. Thus, efforts is expected from all reviewers to make it clear in their critiques their evaluation of the four aspects introduced by the policy.

“Premise” caused confusion. NIH intended for reviewers to consider the scientific foundation of the proposed work. That is, reviewers should critically ask whether the studies or preliminary data leading to the proposed work are scientifically sound. Although this sounds like an obvious consideration, multiple studies, covering multiple fields of science show that scientists have often overestimated how replicable published work is—even when published in top journals. Performing this review of premise can be intellectually demanding and many reviewers did a great job. Others confused “premise” with “scientific significance” or discussed whether the hypotheses of the study were reasonable. Significance refers to the importance of the study; premise refers to its scientific foundation. While a weak premise clearly undercuts the potential significance of a proposal, a strong premise (empirical foundation) does not necessarily make a study significant.

“Sex” was hard to talk about, sometimes. NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in all vertebrate animal and human studies unless there is a compelling scientific argument for not doing so. The impact of this policy varies considerably across different areas of science. Panels were challenged at times to really sort through—

- What is convention, and what is good science?
- What is adequate incorporation of sex in study design?
- Can inclusion of both sexes actually reduce scientific rigor, for example by increasing physiologic variability?
- If a disease affects one sex predominantly but not exclusively, is that sufficient justification for single sex studies?
- What should investigators do with sex specific data that is not sufficient to investigate sex differences beyond reporting it?
There are no blanket answers to such questions at this point, so reviewers need to bring their best scientific thinking to the table in order to achieve the fundamental goal of achieving replicable, generalizable science.

Reviewers know that “obtained from a trusted source” is not an authentication plan. Some applicants still need to be educated on that point. And some fields lack consensus guidelines for crucial resources. However, reviewers—both experienced and expert in their fields—had clear ideas about whether or not the one-page plans were adequate.

Definitions

The scientific premise of the proposed research: The **scientific premise** is the research that is used to form the basis for the proposed research question(s). NIH expects reviewers to evaluate the strengths and weaknesses of the prior research being cited by the applicant to support the application as well as the preliminary data (if applicable). Reviewers’ evaluation of the scientific premise is to be included in the significance criteria.

Rigorous experimental design for robust and unbiased results: **Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. This includes full transparency in reporting experimental details so that others may reproduce and extend the findings. Reviewers are expected to evaluate the strength and weaknesses of the scientific rigor under the approach criterion.

Consideration of relevant biological variables: Biological variables, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response.

NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data or other relevant considerations must be provided for applications proposing to study only one sex.

Authentication of key biological and/or chemical resources: Key biological and/or chemical resources include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. 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; 3. are integral to the proposed research.

The quality of resources used to conduct research is critical to the ability to reproduce the results. Each investigator will have to determine which resources used in their research fit these criteria and are therefore key to the proposed research.

Answers to many frequently asked questions about rigor and transparency can be found on the NIH grants website at [https://grants.nih.gov/reproducibility/faqs.htm#4824](https://grants.nih.gov/reproducibility/faqs.htm#4824).
ADDRESSING SCIENTIFIC PREMISE

**Scientific premise** = the quality and strength of the research used to form the basis for the proposed research question. NIH expects investigators to describe the strengths and weaknesses of the prior research being cited as crucial to support the application. Scientific premise is distinct from the hypothesis or justification.

**Review question:** Is there a strong scientific premise for the project?
- Is appropriate work and/or preliminary data cited?
- Have strengths and weaknesses in prior work in the field been appropriately identified?
- Is the work proposed to fill a significant gap in the field?
- OR has the investigator explained why this is not possible?

**Relationship to Significance:** Instructions for Significance already include consideration of the importance of the problem, critical barriers to progress, how the proposed project will improve scientific knowledge, and how the field will change if the aims are achieved. Scientific premise includes a retrospective consideration of the foundation for the application, rather than a prospective analysis should the aims be achieved.

**Less Effective Comments**
1. The scientific premise is very good. Lacks detail
2. The scientific premise is excellent because the preliminary data show they can do the technique. Speaks to feasibility (Approach), not scientific foundation
3. The scientific premise is well established, given that improved XX would positively impact YY in this population, which would represent a significant advance in treatment. Prospective evaluation of significance, rather than retrospective evaluation
4. Scientific premise is strong given the magnitude of the problem of XX in the YY population. Speaks to importance of the problem, not foundation
5. The scientific premise is that XX will improve YY, which, in turn, will improve response to ZZ. Speaks to the hypothesis
6. The scientific premise of focusing on XX is novel and innovative. Speaks to Innovation

**Effective Comments**
1. The premise is solid and balanced and the study is poised to resolve a long-standing controversy in the field about XYZ.
2. The scientific premise is strong, in that a robust body of preclinical, human laboratory and clinical trial research indicates that XX is implicated in both YY and ZZ.
3. The scientific premise for the project is reasonably sound, based on preliminary studies conducted by the research team and others and what is known about the relationship between XX and YY. However, the lack of a significant effect of XX in the team’s related project is not adequately considered.
4. Scientific premise is supported by high quality studies on XX in YY population and ZZ models.
5. The premise does not acknowledge the equivocal evidence of studies testing XX, the weaknesses of the cited literature, and the limited evidence supporting YY approaches to treat ZZ.
6. The literature reviewed and the preliminary data from an early, very small pilot study are interpreted in an overly ambitious manner, weakening the scientific premise.
7. This study is based on a sound scientific premise. There are only three instruments explicitly designed to study XX, and each of these existing instruments has significant limitations that are well described in the application. The proposed study could therefore help fill an important gap in the field.
8. There were significant weaknesses in terms of scientific premise, as the growing number of studies pointing to minimal effects of XX on YY was not addressed in the application and the application did not clarify how this study would address limitations of previous work in this area.
Related review issues:

• Different research fields may have different best practices for and reach different conclusions about scientific premise and rigor. Assess based on best practices in the field.

• Page limits have not changed. Be alert for page limit violations (e.g. inappropriate use of appendices or other application sections). Alert the SRO if you see a potential issue.

• Page limits, cost and time are not valid reasons to disregard attention to these issues.

• Investigators address rigor and transparency differently (e.g. in labeled sections vs. throughout the research plan). Focus your evaluation on the likely outcome, not grant writing preferences.

• Rigor and transparency considerations apply to R03 (small grant) and R21 (exploratory/developmental) applications. However, preliminary data are not required and the extent to which approach details can be provided may differ. Reviewers should evaluate the scientific merit of these applications, including rigor and transparency, in light of the goals and reviewer guidelines for these activities.
Additional resources

• Rigor and Reproducibility in grant applications (OER site):
  http://grants.nih.gov/reproducibility/index.htm

• NIH presentation of background and goals of Rigor and Transparency (video)
  https://grants.nih.gov/reproducibility/module_1/presentation.html

• Reviewer Guidance on Rigor and Transparency:

• Consideration of Sex as a Biological Variable in NIH-funded Research

• Rigor and transparency do not apply to all applications. See List of Eligible Activity Codes:
  https://nih-extramural-intranet.od.nih.gov/d/sites/default/files/RigorActivityCodes-20151006.pdf. Also, certain Funding Opportunity Announcements are exempt from Rigor and Transparency, by request from the ICs.

• Questions about the NIH policy should be directed to reproducibility@nih.gov