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NIH Rigor and Transparency Guidance

The NIH recently implemented updates to research grant and career development award applications aimed at enhancing reproducibility through rigor and transparency with a focus on four areas: scientific premise, rigorous experimental design, consideration of relevant biological variables, and authentication of key biological and/or chemical resources.

Investigators will need to consider how these four areas apply to their proposed research in the grant application. NIH expects the applicants to describe how they will achieve robust and unbiased results when describing the experimental design and proposed methods. Robust results are obtained by using methods designed to avoid bias and can be reproduced under well-controlled and reported experimental conditions.

NIH defines **scientific rigor** as *the strict application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation, and reporting of results. Scientific rigor also includes transparency in reporting full experimental details so that others may reproduce and extend the findings.*

Additional rigor and transparency questions reviewers will be asked to consider when reviewing applications

- Significance - Is there a strong scientific premise for the project
- Approach - Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

Additional Review Considerations

- 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.

Scientific Premise:

Applications often include data aimed at demonstrating the feasibility of the proposed experimental approach. While this type of data can be important as proof of concept, it does not speak to the project's scientific premise – the strengths and weakness of the data and previously performed work upon which the proposal is built upon.

A hypothetical example might help clarify this point. Let's say an application proposes to investigate whether and how enzyme A regulates a particular cell function. Preliminary data

suggest that enzyme A modifies protein B, and there are data in the literature showing that protein B regulates the particular cell function in question. The strength of the proposed project is dependent on the strength of the data suggesting that protein B regulates the particular cell function. Thus, the new application instruction pertaining to premise calls for "consideration of the strengths and weaknesses of published research or preliminary data" to evaluate the rationale for investigating the effects of enzyme A on the particular cell function. Without this information, the scientific premise of the proposed experiment may be built on shaky grounds.

Therefore, as a part of the Significance section of the Research Strategy, the updated instructions clarify that applicants should: "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." Weaknesses in scientific rigor or gaps in transparency that preclude the assessment of scientific rigor should be acknowledged. If such weaknesses are identified, the applicant should consider whether or not to include this data in support of the application and how the proposed research will address the weaknesses.

It is important to stress that attention to scientific premise does not impede innovation. Even though innovative research is inherently risky, consideration of scientific premise can help investigators identify the risks and develop a research strategy that enhances the opportunity for success.

Scientific Rigor:
Scientific rigor - the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results. In published papers, full transparency in reporting experimental details is crucial for others to assess, reproduce, and extend the findings. Likewise, in grant applications, full transparency is necessary for reviewers to properly assess the proposed studies.

Therefore, as part of the Approach section of the Research Strategy, updated instructions clarify this expectation to emphasize how the experimental design and methods proposed will achieve robust and unbiased results. Solid, well controlled experiments can produce robust results capable of being reproduced under well-controlled conditions using reported experimental details. A robust approach might include use of appropriate statistical methods, prospective sample size estimation, replicates, or standards (for example, reference reagents or data standards). Robust and credible results are those obtained with methods specifically designed to avoid bias, such as blinding, randomization, and prospectively defined exclusion/inclusion criteria, to name a few.

It is important to keep in mind that each scientific field may have its own set of best practices or standards to achieve scientific rigor. Reviewers are well-positioned to identify strengths or weaknesses of the proposed plans. Applicants are encouraged to include a succinct description of the experimental design and methods with enough detail to assure the reviewers that the necessary elements of rigor will be addressed.

Consideration of Relevant Biological Variables:
As with sex, the clarifying instructions on consideration of relevant biological variables do not prescribe that the biological variable itself be studied. If biological variables are known to affect a

system or disease model proposed for study, the application should discuss how you will control for these factors, if necessary.

Updated instructions for the Approach section of the Research Strategy ask the applicant to: 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.
What are some biological variables, other than sex, that might need to be considered when doing research in vertebrate animals? Let's start with an example of early vaccine development in mice. It's been well-established that C57BL/6 and Balb/c strains of mice produce different immune responses due to differing genetic backgrounds. Therefore, if an application proposes to study an immune response in mice, it may be necessary to indicate which strain will be used and why. Other variables that might be important include the vendor source or supplier, the age of the animals, since both can affect immune responses. Depending on the field and the research question, housing conditions may need to be considered, including the room temperature and light/dark cycles. Studies with mouse tissues or primary cells should also consider relevant biological variables, including sex, in proposing and reporting research.

The NIH has already established that sex must be considered in proposing studies in humans. Other biological variables that may need to be considered include age, body mass index (BMI), socioeconomic status, or underlying health conditions. Many clinical studies already take these variables into account, but it is important that observations be reported. Variables such as sex, age, BMI, and underlying health conditions may also need to be considered when proposing and reporting studies with human biological samples, including blood and tissue. Consideration of other variables is critical to enable reviewers and the scientific community to assess the internal validity of a study – whether the findings hold up after accounting for confounding and selection biases – and the external validity of a study – whether the findings, even if internally valid, apply to the "real world."

Authentication of Key Biological and/or Chemical Resources:
Research performed with unreliable or misidentified resources can negate years of hard work and eliminate any chance for a study to be reproduced or expanded upon. For this reason, it is imperative that researchers regularly authenticate key resources used in their research.

Updated application instructions under "Additional Attachments (SF424 12)" ask the applicant to: *Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.*

- 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.

The authentication plan should be included as an additional attachment (not as part of the research strategy), and it should state, **in one page or less**, how you will authenticate key resources, including the frequency, as needed for your proposed research. The resources that require authentication will vary depending on the reagent/resource and the experimental context in which it will be used. You do not need to provide authentication data itself in this one page attachment; reviewers will be asked to assess the adequacy of the plans you propose for authenticating key resources.

Purchased or established resources may have been authenticated prior to receipt, and the vendor may have included a specification sheet with the product. If the authentication data provided by the vendor meets your needs in terms of how the product will be used, this may be mentioned this in the plan, but you should also include a plan to independently verify the identity and activity of the product before use. If the product will be used long-term, consider the stability of the product and how the validity of the product will be assessed over time.

Researchers are encouraged to learn more about the new NIH research grant and RPPR application guidelines by visiting the following NIH websites:

Resources:

NIH Extramural Nexus posts:

- Updates on Addressing Rigor in Your NIH Applications
- Consideration of Relevant Biological Variables in NIH Grant Applications
- Scientific Rigor in NIH Grant Applications
- Authentication of Key Biological and/or Chemical Resources in NIH Grant Applications
- What Kind of Information Should I Include in My Application's Resource Authentication Plan?

NIH Training Module on Rigor and Transparency
Rigor and Reproducibility
NIH FAQs on Reproducibility

NIH NOT-OD-16-011 - Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications
NIH NOT-OD-16-012 - Implementing Rigor and Transparency in NIH & AHRQ Career Development Award Applications
NIH NOT-OD-16-058 - NIH & AHRQ Grant Application Changes for Due Dates On or After January 25, 2016

Research Performance Progress Report (RPPR) RPPR Information
SF424 Instructions