

Changes to NIH Grant Elements

NIH recently implemented updated requirements to research grant and career development award applications aimed at enhancing reproducibility through rigor and transparency with a focus on four areas: (1) scientific premise, (2) rigorous experimental design, (3) consideration of relevant biological variables (sex *and* other elements as biological variables), and (4) authentication of key biological and/or chemical resources. Applications submitted for due dates on or after January 25, 2016 are required to address these elements.

The NIH Rigor and Reproducibility in Applications [webpage](#) is most consolidated source of information on how to address these issues. One useful [link](#) within that page is an ~ 30 minute, 45 slide training module that better explains the criteria. Another useful link is the [Rigor and Transparency FAQ](#) page. [Table 1 \(following\)](#) provides a summary of the [information in these sites](#). However, it is likely worth your time to review these in detail.

It may be helpful to understand the background that elicited these updated requirements and that is disbursed across the NIH website in numerous webpages including: Dr. Michael Lauer’s (NIH’s Deputy Director for Extramural Research) [blog](#). See: 10/30/15: [Standards](#); 1/11/16: [Rigor](#); 1/28/16: [Scientific Premise](#); 1/29/16: [Biological Variables](#); 1/29/16: [Authentication of Resources](#). Much of what is presented therein is summarized in Table 1, as is how each of the four elements are to be addressed within an application, and how the elements will be scored.

Not directly provided is specific instructional details. For instance, should there be headings for each element? How much detail is needed/expected? Isn’t much (all, except for the newly added key biological and/or chemical resources page) of this being provided in high-quality (i.e. funded) submissions already? Note that no added space will be provided within the Research Strategy to accommodate the supplemental discussion. However, at least for the rigor element, [examples of succinct text](#) are available.

Here are [possible options](#) to meet the requirements that can/will likely change as reports from study sections become available.

- “Scientific premise”: a separate and titled sub-section be included in *Significance*.
- “Rigor”: to be included within multiple areas of the proposal.
 - Although the instructions state that “rigor” be applied to the *Approach* section. The description of the element clearly states usefulness in *Background & Significance* (interpretation of others work) and discussing any preliminary data provided. As stated, “any weaknesses or gaps in rigor, or reporting on rigor, should be acknowledged, along with a plan to address those gaps going forward.”
 - Within each specific aim’s *Expected results and alternative outcomes and approaches* section (and thus possibly renamed: *Expected results, alternative outcomes and approaches, and application of rigor*).
 - Within any discussion of methodology.
- “Biological variability”: to be acknowledged throughout the *Approach* stating use of male and female animals and importantly, how data will be statistically analyzed related to sex. Strong rationale is required if only one sex is to be used. **Note** that sex is not the *only* consideration for this element: age, weight, and underlying health conditions, are often critical factors affecting health or disease and need to be discussed.
- “Key biological resources”: a separate attachment. It is important to include all resources but remain specific to *authentication*. Using this space to extend the page limits of the Research Strategy, i.e. to include preliminary data, is entirely prohibited.

Table 1: Summary of new elements and review criterion.

Element	Definition	Updated Instructions	Updated Review Criterion
Scientific Premise	The research that is used to form the basis for the proposed research question(s). NIH expects applicants to describe the general strengths and weaknesses of the prior research being cited by the applicant as crucial to	Include “Scientific Premise” in the <i>Significance</i> section to include, “Description of the scientific premise of the proposed project, including consideration of the strengths and weaknesses of published research or	<i>Scored criterion.</i> Is there a strong scientific

	support the application. It is expected that this consideration could include attention to <i>rigor</i> of experimental designs, as well as the incorporation of relevant <i>biological variables</i> and <i>authentication of key resources</i> .	preliminary data crucial to the support of your application.”	premise for the project?
Scientific Rigor	<p>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 of experimental details so that findings may be reproduced and extended.</p> <p><i>Examples of experimental design to report:</i></p> <ul style="list-style-type: none"> • Use of standards • Sample size estimation • Randomization • Blinding • Appropriate replicates • Controlling for inter-operator variability • Statistical methods planned • Inclusion/exclusion criteria • Subject retention and attrition • How missing data will be handled • Others 	Include “Scientific Rigor” in the <i>Approach</i> section to describe the experimental design and methods proposed and they will achieve robust and unbiased results.	<i>Scored criterion.</i> Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
Biological Variables	Inclusion of 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.	<p>Include “Biological Variables (sex)” in the <i>Approach</i> section to describe the experimental design methods proposed and how they will achieve robust and unbiased results.</p> <p>See NOT-OD-15-102 in Table 2 below.</p>	<p><i>Scored criterion.</i> Have the investigators presented appropriate strategies to ensure robust and unbiased approach for the work proposed?</p> <p>Have investigators presented adequate plans to address biological variables, such as, but not limited to, sex?</p>

<p>Key biological and/or chemical resources</p>	<p>Include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Key biological and/or chemical resources:</p> <ul style="list-style-type: none"> • May differ from laboratory to laboratory or over time; • May have qualities and/or qualifications that could influence the research data; • Are integral to the proposed research; and • Are not limited to resources generated with NIH funds. <p>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.</p>	<p>This is a new PDF attachment to be included with the overall submission.</p> <p>Information in this section must focus <i>only</i> on authentication and/or validation of key resources to be used in the study; all other methods and preliminary data must be included within the page limits of the Research Strategy.</p> <p>See: NOT-OD-16-011 in Table 2 below</p>	<p><i>Not a scored criterion.</i> For projects involving key biological and/or chemical resources, reviewers will comment on the plans proposed for identifying and ensuring the validity of those resources.</p>
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Table 2 is a list/guide that provides the specific NIH notices that explicitly layout the new criteria. Provided in the table is a content summary. It is suggested and may be necessary to review the entire notice for details/nuance. Also found in the table are links to published articles that further describe the policy stated in each notice. These articles may also be worth reviewing. Lastly, also included in Table 2 are notices not directly related to the new policy of enhancing reproducibility through rigor and transparency, but are updates to grant production. These include updated criteria for “simplification” of the Vertebrate Animal Section (NOT-OD-16-006) and use of fonts (NOT-OD-16-009).

Table 2. Relevant NIH Announcements:

<p>NIH Announcement # / Release Date</p>	<p>Content Summary</p>
<p>NOT-OD-15-102 6/9/15</p>	<p><i>Consideration of Sex as a Biological Variable in NIH-funded Research</i></p> <p>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. Further information regarding NIH expectations for the consideration of sex as a biological variable is available. See also Clayton and Collins. 2014. Nature. 509: 282-283.</p>
<p>NOT-OD-15-103 6/9/15</p>	<p><i>Enhancing Reproducibility Through Rigor and Transparency</i></p> <p>This notice is the initial announcement stating the <i>rigor</i> issue. This has come to the forefront because recent attention on the inability to reproduce or extend research findings reported in some peer-reviewed literature. This led the NIH leadership to publish a commentary on possible causes and potential NIH actions.</p>
<p>NOT-OD-16-004 10/13/15</p>	<p>This is the initial announcement that informs the biomedical and health services research communities of planned changes to policies, forms and instructions for grant applications submitted in 2016. This notice may be helpful to review since it provides an overview with links to other relevant notices that provide “specific” guidance.</p> <p>The planned changes focus on the following areas:</p> <ul style="list-style-type: none"> • Rigor and transparency in research

	<ul style="list-style-type: none"> • Vertebrate animals • Inclusion reporting • Data safety monitoring • Research training • Appendices • Font requirements • Biosketch clarifications
<p>NOT-OD-16-006 10/13/15</p>	<p><i>Simplification of the Vertebrate Animals Section</i></p> <p><i>Review content of notice.</i> The intent is to remove redundant (to the Specific Aims) information from the VAS. For instance, it is stated that “Justification for the number of animals has been eliminated.” My interpretation is that this is eliminated from the VAS but not the grant as a whole. Good grantsmanship dictates that this information be maintained. Similarly stated is that “A description of veterinary care is no longer required.” A suggestion is to move existing used text to the <i>Facilities</i> section.</p>
<p>NOT-OD-16-009 10/13/15</p>	<p><i>Font Guidelines</i></p> <p>Additional flexibility regarding the fonts used in PDF attachments included in grant applications submitted on or after May 25, 2016.</p> <p>Do not ignore readability, etc. IE Just because you can doesn't mean you should.</p>
<p>NOT-OD-16-011 10/9/15</p>	<p><i>Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications</i></p> <p>See NOT-OD-15-103 6/9/15 and NOT-OD-16-004 10/13/15 above.</p> <p>16-011 adds information regarding timeline and included grant activity codes.</p> <p><u>More importantly</u>, 16-011 states that the <i>Significance</i> and <i>Approach</i> sections of the Research Strategy need to also include:</p> <p>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.</p> <p>Approach Describe the experimental design and methods proposed and how they will achieve robust and unbiased results. Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans. Refer to NOT-OD-15-102 6/9/15 above for further clarification.</p> <p>It also codifies the “New Authentication of Key Biological and/or Chemical Resources” Attachment. See also, Lorsch, et al. 2014. Science. 346: 1452-1453.</p> <p>It also defines scoring/review criteria:</p> <p>Significance Is there a strong scientific premise for the project?</p> <p>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?</p> <p>Authentication of Key Biological and/or Chemical Resources</p>

	<p>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.</p> <p>Finally, it states that RPPR submissions will need to adhere to the increased rigor standards. Fully defined in NOT-OD-16-031 12/15/15 below.</p>
<p>NOT-OD-16-031 12/15/15</p>	<p><i>Research Performance Progress Reports (RPPR) to Address Rigor and Transparency</i></p> <p>Rigor and Transparency standards will be applied for RPPRs due on or after January 25, 2016.</p> <p>Additions include: 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.</p>
<p>NOT-OD-034 12/17/15</p>	<p><i>Formal Instruction in Rigorous Experimental Design and Transparency to Enhance Reproducibility</i></p> <p>Timeline for Institutional Training Grants, Institutional Career Development Awards, and Individual Fellowships</p>