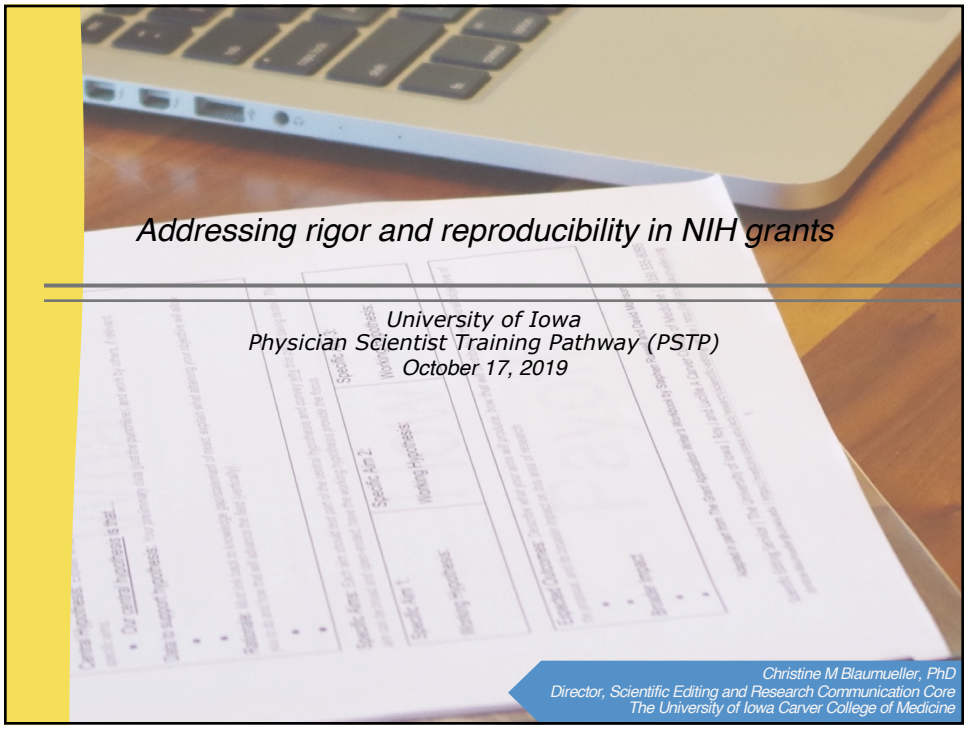

Addressing rigor and reproducibility in NIH grants

University of Iowa
Physician Scientist Training Pathway (PSTP)
October 17, 2019

Christine M Blaumueller, PhD
Director, Scientific Editing and Research Communication Core
The University of Iowa Carver College of Medicine

UI Carver College of Medicine
Scientific Editing and Research Communication Core

Let us help you make your message clear, concise, and compelling.

Advice based on our extensive experience in laboratory research and editing of scientific content. Services include:

- Detailed input on writing projects – emphasis on grants and manuscripts
- One-on-one consultation on writing strategy
- Teaching of interactive courses, workshops, and seminars on scientific writing
- Grant Planning Forums

Our efforts have facilitated success:

- Garnering funding
- Publishing in high-quality journals

Phone: 319-335-8095
Email: COM-ScientificEditing@uiowa.edu
Web: medicine.uiowa.edu/editingcore

Activities:

- Provide input on drafts of writing projects
- Provide consultation on writing strategy
- Teach scientific writing
- Brainstorm with authors on projects
- Collect and generate resources
- Liaise with other RD professionals

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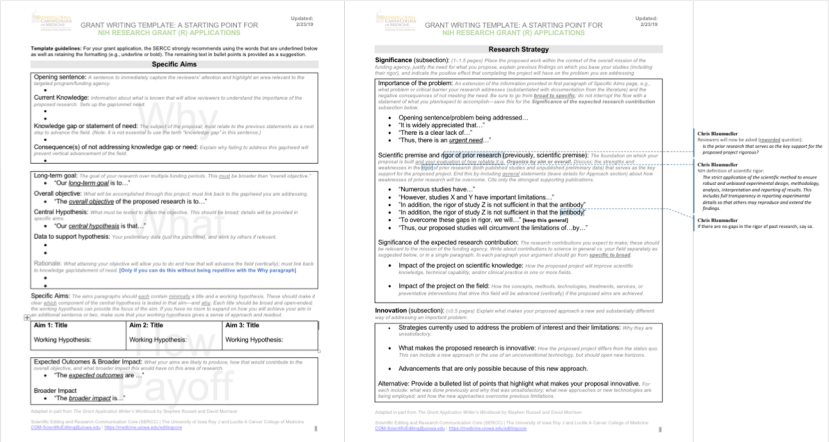
- Collect and generate resources
  - Changes in funding agency requirements
  - Grant writing templates (NIH "R" and "F" grants)
- Liaise with other RD professionals

Will make PDF file of talk available …

... and tell you about our writing resources

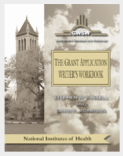


https://medicine.uiowa.edu/sercc/resources/writing-grants

Topics

Evolution of NIH requirements & scored review criteria

Our recommendations



Other recommendations

Additional examples and other resources

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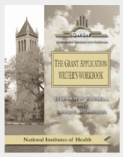


Other recommendations

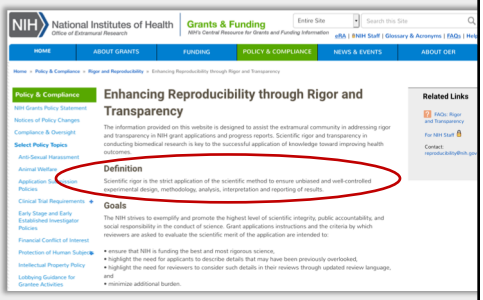
Additional examples and other resources

Recent Changes in NIH Requirements

- 2010
  - Shortened Research Strategy by 50%
  - "Background and Significance" –> "Significance"
  - "Innovation" section added
- 2016
  - Required evidence of rigor and reproducibility, including:
    - Discussion of ***scientific premise*** within Significance section
    - Discussion of ***rigor of proposed research*** in Approach
    - Discussion of ***biological variables*** in Approach
    - Explanation of ***how key resources will be authenticated*** (attachment)
- 2019
  1. Changed ***scientific premise*** to ***weaknesses in rigor of prior research***
  2. Requires discussion of ***how weaknesses in rigor of prior research will be addressed*** in Approach

NIH definition of scientific rigor (2019)…

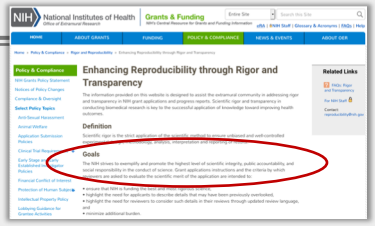
- *strict application of the scientific method*
- *to ensure unbiased and well-controlled*
  - *— experimental design*
  - *— methodology*
  - *— analysis*
  - *— interpretation*
  - *— reporting of results*



https://grants.nih.gov/policy/reproducibility/index.htm

Posted 11/27/18

Goals of NIH policy (2019)…



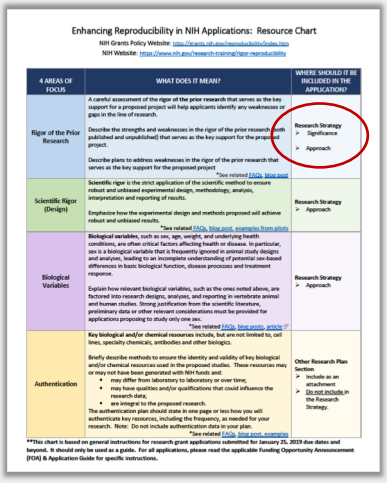
- *Exemplify and promote the highest level of:*
  - *scientific integrity*
  - *public accountability*
  - *social responsibility*

  in the conduct of science.
- *Grant applications instructions and the criteria by which reviewers are asked to evaluate the scientific merit of the application are intended to:*
  - *ensure that **NIH** is funding the best and most rigorous science*
  - *highlight the need for **applicants** to describe details that may have been previously overlooked*
  - *highlight the need for **reviewers** to consider such details in their reviews through updated review language*
  - *minimize additional burden*

https://grants.nih.gov/policy/reproducibility/index.htm

Posted 11/27/18

New NIH guidelines – for submission from Jan 25, 2019



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https://grants.nih.gov/policy/reproducibility/guidance.htm

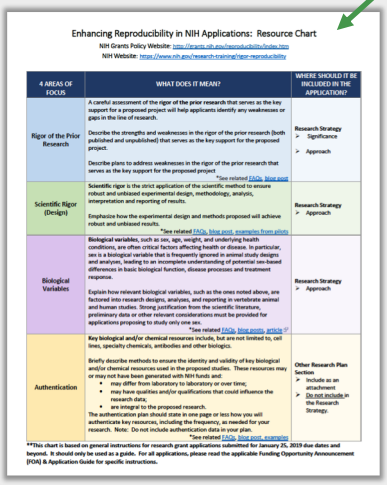
Updated November 26, 2018

- *The application instructions and review criteria will be clarified to*
  - *replace the term "scientific premise" [in Significance]*
  - *with the term "rigor of the prior research".*
- *Applicants will also be instructed to describe plans to address any weaknesses in the rigor of prior research within the Research Strategy.*
- *For additional details, see NOT-OD-18-228 and NOT-OD-18-229.*

2016: *Justification of need for proposed research, e.g.* ***limitations*** *of previous studies*

2019: *Previous failure to apply good scientific method* ***(lack of rigor)***

Rigor of prior research – Instructions and Expectations



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   - See related FAQs, Blog Post
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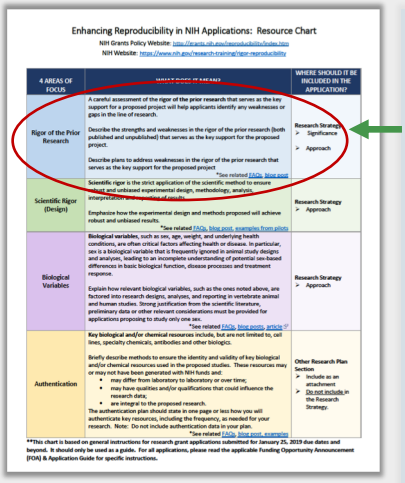
https://grants.nih.gov/policy/reproducibility/guidance.htm
Updated November 26, 2018

Rigor of prior research – *Instructions*



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- *[In **Significance** section]*
  Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project.
- *[In **Approach** section]*
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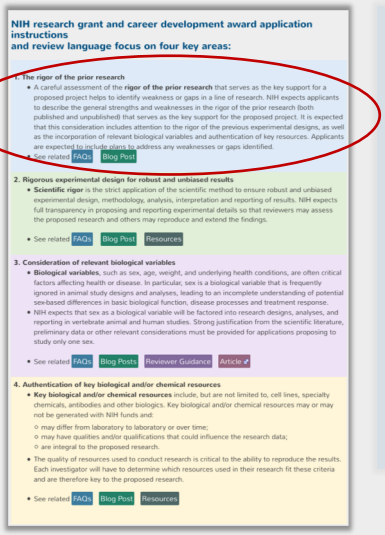
https://grants.nih.gov/policy/reproducibility/guidance.htm
Updated November 26, 2018

Rigor of prior research – *Expectations*

2019: *Assessment of **prior research** should include…*



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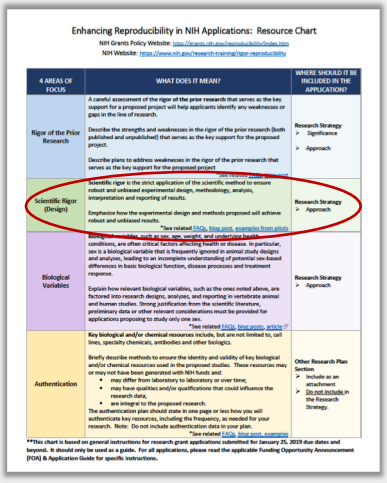
Significance

Approach

https://grants.nih.gov/policy/reproducibility/guidance.htm
Updated November 26, 2018

Scientific rigor (proposed research) – *Instructions*



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- *In **Approach** section:*

  Emphasize how the experimental design and methods proposed will achieve robust and unbiased results.

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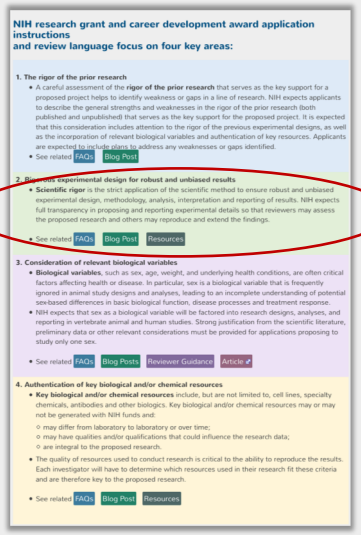
Updated November 26, 2018

Scientific rigor (proposed research) – *Expectations*



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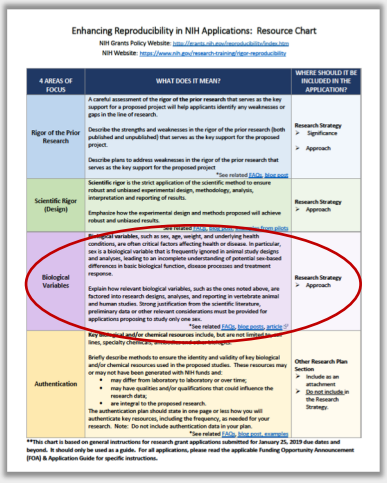
Biological variables – *Instructions*



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NIH Website: https://www.nih.gov/research-training/rigor-reproducibility

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Rigor of the Prior Research	A careful assessment of the rigor of the prior research that serves as the key support for a proposed project will help applicants identify any weaknesses or gaps in the line of research. Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project. Describe plans to address weaknesses in the rigor of the prior research that serves as the key support for the proposed project. *See related FAQs, blog post	Research Strategy ➢ Significance ➢ Approach
Scientific Rigor (Design)	Scientific rigor is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Emphasize how the experimental design and methods proposed will achieve robust and unbiased results. *See related FAQs, blog posts, Resources, Policy	Research Strategy ➢ Approach
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. Explain how relevant biological variables, such as the ones noted above, are 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. *See related FAQs, blog posts, article	Research Strategy ➢ Approach
Authentication	**Key biological and/or chemical resources** include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. These resources may or may not have been generated with NIH funds and: ▪ 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. The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research. Note: Do not include authentication data in your plan. *See related FAQs, blog post, examples	Other Research Plan Section ➢ Include as an attachment ➢ Do not include in the Research Strategy.

**This chart is based on general instructions for research grant applications submitted for January 25, 2019 due dates and beyond. It should only be used as a guide. For all applications, please read the applicable Funding Opportunity Announcement (FOA) & Application Guide for specific instructions.

https://grants.nih.gov/policy/reproducibility/guidance.htm
Updated November 26, 2018

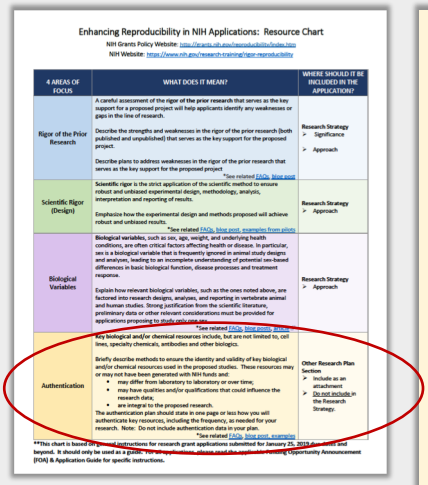
***Biological variables**, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease.*

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.

- *In **Approach** section:*
  Explain how relevant biological variables, such as the ones noted above, are 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 – *Instructions*



Enhancing Reproducibility in NIH Applications: Resource Chart

NIH Grants Policy Website: https://grants.nih.gov/reproducibility/index.htm
NIH Website: https://www.nih.gov/research-training/rigor-reproducibility

4 AREAS OF FOCUS	WHAT DOES IT MEAN?	WHERE SHOULD IT BE INCLUDED IN THE APPLICATION?
Rigor of the Prior Research	A careful assessment of the **rigor of the prior research** that serves as the key support for a proposed project will help applicants identify any weaknesses or gaps in the line of research. Describe the strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project. Describe plans to address weaknesses in the rigor of the prior research that serves as the key support for the proposed project *See related FAQs, blog post	Research Strategy ➢ Significance ➢ Approach
Scientific Rigor (Design)	Scientific rigor is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Emphasize how the experimental design and methods proposed will achieve robust and unbiased results. *See related FAQs, blog post, examples from pilots	Research Strategy ➢ Approach
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. Explain how relevant biological variables, such as the ones noted above, are 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. *See related FAQs, blog posts, Policy	Research Strategy ➢ Approach
Authentication	**Key biological and/or chemical resources include**, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. These resources may or may not have been generated with NIH funds and: ▪ 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. The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research. Note: Do not include authentication data in your plan. *See related FAQs, blog post, examples	Other Research Plan Sections ➢ Include as an attachment ➢ Do not include in the Research Strategy.

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Updated November 26, 2018

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These resources may or may not have been generated with NIH funds and:

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- *may have qualities and/or qualifications that could influence the research data;*
- *are integral to the proposed research.*

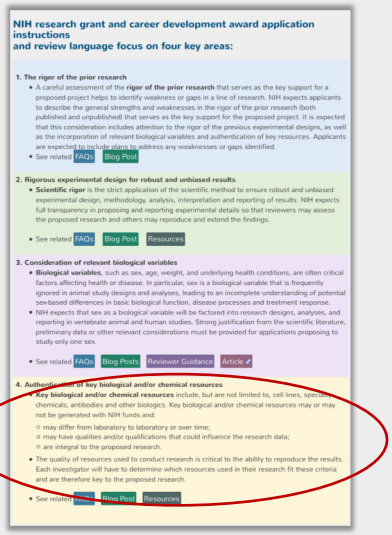
The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research.

Note: Do not include authentication data in your plan.

https://grants.nih.gov/policy/reproducibility/guidance.htm
Updated November 26, 2018

Authentication – *Expectations*

Separate attachment



NIH research grant and career development award application instructions and review language focus on four key areas:

1. The rigor of the prior research
- A careful assessment of the **rigor of the prior research** that serves as the key support for a proposed project helps to identify weakness or gaps in a line of research. NIH expects applicants to describe the general strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project. It is expected that this consideration includes attention to the rigor of the previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources. Applicants are expected to include plans to address any weaknesses or gaps identified.
- See related FAQs Blog Post

2. 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. NIH expects full transparency in proposing and reporting experimental details so that reviewers may assess the proposed research and others may reproduce and extend the findings.
- See related FAQs Blog Post Resources

3. 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.
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- See related FAQs Blog Posts Reviewer Guidance Article

4. 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:
  - 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.
- 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.
- See related FAQs Blog Post Resources

***Key biological and/or chemical resources include**, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics.*

Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

These resources may or may not have been generated with NIH funds and:

- *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*

[Because] The quality of resources used to conduct research is critical to the ability to reproduce the results…

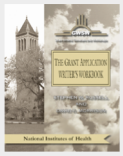
Each investigator will have to determine which resources used in their research fit these criteria and are therefore key to the proposed research.

Topics

NIH National Institutes of Health
Turning Discovery Into Health

Evolution of NIH requirements & scored review criteria

Our recommendations



Other recommendations

Additional examples and other resources

Adapting to Change

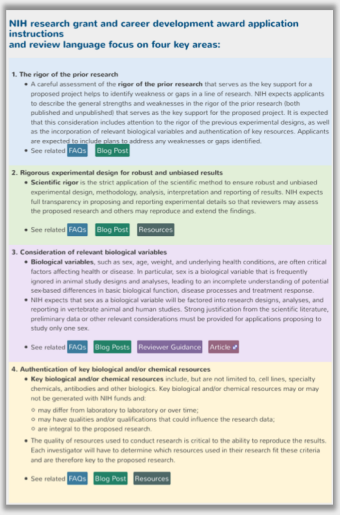
- What we look for: Are sections addressing new requirements included?
- DSP may recommend changes if key-word searches unsuccessful

Significance

- Weaknesses in rigor of *prior research*

Approach

- How weaknesses in rigor of *prior research* will be addressed
- How rigor of *proposed research* will be ensured
- Consideration of biological variables, including sex, in the proposed research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- See related FAQs Blog Post Resources

3. Consideration of relevant biological variables
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- See related FAQs Blog Post Resources

https://grants.nih.gov/policy/reproducibility/guidance.htm
Updated November 26, 2018

Scored Review Criteria – Significance 2016

1) Does the project address an important problem or a critical barrier to progress in the field?

2) Is there a strong scientific premise for the project?

3) If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

4) How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Our Recommendations – Significance 2016

Importance of the problem and/or critical barriers to progress

Scientific premise (organize overall or by aim)*

Significance of the expected research contribution

- Impact of the project on scientific knowledge / technical capability / clinical practice
- Impact of the project on the field

Previously: 0.5-0.75 pp

- *Review of literature; validation of importance of problem*
- *Statement of significance of problem*
- *Discussion of study benefits*

For 3 aims, 1–1.5 pages

* **The relevant literature:** Strengths and weaknesses

- Rigor of study design (e.g. statistical power, blinded analysis)
- Incorporation of relevant biological variables (e.g. detail regarding sex)

Your preliminary data that contribute to scientific foundation of proposal.

Our Recommendations – Significance 2016

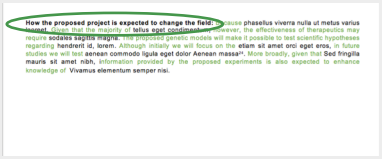

RESEARCH STRATEGY

Significance

Importance of the problem:

Scientific premise:

How the proposed project will improve scientific knowledge:


How the proposed project is expected to change the field:

R21:
4th percentile

Scored Review Criteria – Significance 2019

1) Does the project address an important problem or a critical barrier to progress in the field?

Is there *a strong scientific premise* for the project? (2016)

2) Is the prior research that serves as the key support for the proposed project rigorous?

3) If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

4) How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Our Recommendations – Significance 2016

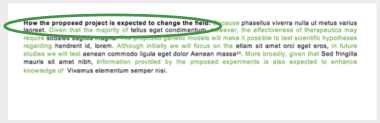
RESEARCH STRATEGY

Significance

Importance of the problem:

Scientific premise:

How the proposed project will improve scientific knowledge:



How the proposed project is expected to change the field:

New approach is similar

but

shift focus of scientific premise to *include rigor of past research*.

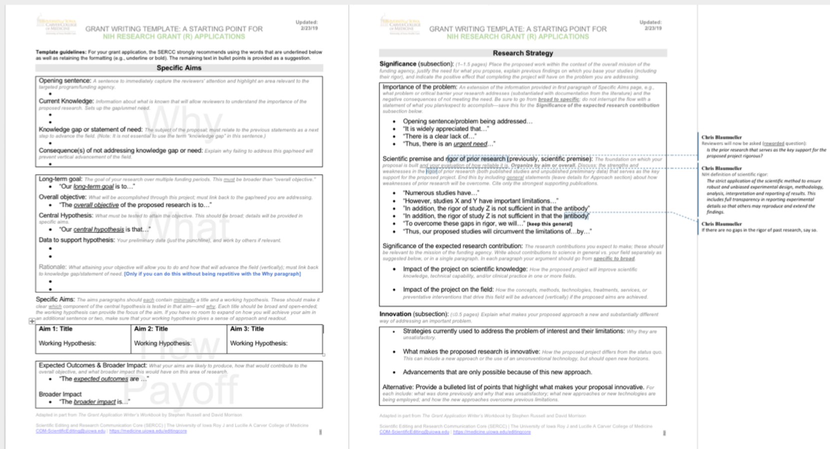
Our Recommendations – Significance

Include a statement directly addressing the rigor of prior research

1) Importance of the problem and/or critical barrier to progress
2) Scientific premise and rigor of the prior research (organize overall or by aim)*
   - Numerous studies have…
   - However, studies X and Y have important limitations…
   - In addition, the rigor of study Z is not sufficient in that the antibody was not tested on…
   - To overcome these gaps in rigor, we will… [keep this general here]
   - Thus, our proposed studies will circumvent the limitations of… by …
3) Significance of the expected research contribution
   - Impact of the project on scientific knowledge / technical capability / clinical practice
   - Impact of the project on the field

OR: The previous studies were rigorous. Nevertheless, they were limited in that….

Grant writing templates as resource…


GRANT WRITING TEMPLATE: A STARTING POINT FOR NIH RESEARCH GRANT (R) APPLICATIONS

Specific Aims

GRANT WRITING TEMPLATE: A STARTING POINT FOR NIH RESEARCH GRANT (R) APPLICATIONS

Research Strategy

https://medicine.uiowa.edu/sercc/resources/writing-grants

Scored Review Criteria – Approach 2016

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Have the investigators presented strategies to ensure *a robust and unbiased approach*, as appropriate for the work proposed? (2016)
- Are potential problems, alternative strategies, and benchmarks for success presented?
- If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
- Have the investigators presented *adequate plans to address relevant biological variables*, such as sex, for studies in vertebrate animals or human subjects? (2016)
- If the project involves human subjects and/or NIH-defined clinical research, are the plans for: protections for human subjects, and inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, …?

Our Recommendations – Approach pre-2016

Approach

- For each aim
  - Title of Specific Aim
  - Introduction/rationale paragraph
  - Justification and Feasibility paragraph (including background and preliminary data)
  - Research Design paragraphs
  - Expected Outcomes paragraph
  - Potential Problems and Alternative Strategies paragraph
- Timeline and Benchmarks for success
- Future Directions

Our Recommendations – Approach 2016

Approach

- For each aim
  - Title of Specific Aim
  - Introduction/rationale paragraph
  - Justification and Feasibility paragraph (including background and preliminary data)
  - Research Design paragraphs
  - Expected Outcomes paragraph
  - Potential Problems and Alternative Strategies paragraph
- Timeline and Benchmarks for success
- Future Directions

Included figures in support of scientific premise – Keep this structure

Our Recommendations – Approach pre-2016

Approach

- For each aim
  - Title of Specific Aim
  - Introduction/rationale paragraph
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  - Research Design paragraphs
  - Expected Outcomes paragraph
  - Potential Problems and Alternative Strategies paragraph
- Timeline and Benchmarks for success
- Future Directions

Research Design Paragraphs:
- Approach to be used
- Overview of methods used
- Essential minor/major equipment
- Detailed expectations
- How results will be interpreted

Our Recommendations – Approach 2016

Approach

- Rigor of *proposed research*
- Consideration of biological variables including sex

Separate paragraphs or combined

- For each aim
  - Title of Specific Aim
  - Introduction/rationale paragraph
  - Justification and Feasibility paragraph (including background and preliminary data)
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- Future Directions

Our Recommendations – Approach pre-2016

Approach

- For each aim
  - Title of Specific Aim
  - Introduction/rationale paragraph
  - Justification and Feasibility …
    (including background and preliminary data)
  - Research Design paragraphs
  - Rigor of proposed research
  - Consideration of biological variables including sex

  Separate paragraphs or combined
  - Expected Outcomes paragraph
  - Potential Problems and Alternative Strategies paragraph
- Timeline and Benchmarks for success
- Future Directions

Our Recommendations – Approach pre-2016

Approach

- Rigor of proposed research
- Consideration of relevant biological variables including sex
- For each aim
  - Title of Specific Aim
  - Introduction/rationale paragraph
  - Justification and Feasibility paragraph
    (including background and preliminary data)
  - Research Design paragraphs
  - Expected Outcomes paragraph
  - Potential Problems and Alternative Strategies paragraph
- Timeline and Benchmarks for success
- Future Directions

Regardless of which format you choose to use, include:

1. ***Rigor of proposed research*** *–> robust, unbiased results (discuss any of the categories below that apply)*
   - *Randomization protocol for sample groups, inclusion/exclusion criteria*
   - *Blinded data recording and analysis*
   - *Controls and replicates needed*
   - *Sample-size estimation/power analysis (critical for studies using human subjects and higher vertebrates)*
   - *Principles of good laboratory practice*
   - *Essential reagents and their authentication*
   - *Statistical analyses to be used*
   - *Controls and replicates needed*
2. ***Relevant biological variables including sex***
   - *Sex (equal numbers of each; impact on results; separate analysis of effects; karyotype of cell lines)*
   - *Weight, age, health status, body mas index, underlying comorbid conditions…*

Adapted from Landis SC et al. (2012) A call for transparent reporting to optimize the predictive value of preclinical research. *Nature* Oct. 11; 490(7419):181-91

Scored Review Criteria – Approach 2019

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Have the investigators presented strategies to ensure *a robust and unbiased approach*, as appropriate for the work proposed? (2016)
- Have the investigators included plans to *address weaknesses in the rigor of prior research* that serves as the key support for the proposed project? (2018)
- Are potential problems, alternative strategies, and benchmarks for success presented?
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Our Recommendations – Approach 2019

Approach

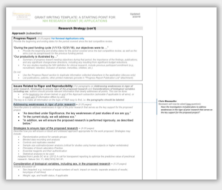
- Issues related to rigor and reproducibility
  - Addressing weaknesses in rigor of prior research
  - Strategies to ensure rigor of proposed research
  - Consideration of biological variables including sex

Separate paragraphs or combined

- Aim x (for each aim)
  - Title of Specific Aim
  - Introduction/rationale paragraph
  - Justification and Feasibility paragraph (including background and preliminary data)
  - Research Design paragraphs
  - Expected Outcomes paragraph
  - Potential Problems and Alternative Strategies paragraph
- Timeline and Benchmarks for success
- Future Directions

To do this well:

Need to specify what weaknesses are earlier (in Significance section)



Example of Robust and Unbiased Approach 2016

R37 Renewal, scored in 2nd percentile – New subsection (after Aim 3)

Research Rigor and Transparency: *Scientific rigor and reproducibility is maintained when opportunities for error are minimized through education of the team members about potential sources of error. To this end, the PI, staff, and students consult a Biostatistics and Research Design Core within the UI Institute for Clinical and Translational Sciences in the methodological planning of research protocols. This ensures robust statistical outcomes and post-experimental analysis of data. The PI and all associated personnel have also received NIH-mandated ethics training. All data will be reviewed by multiple team members to ensure its validity and to minimize operator biases; this occurs formally at twice weekly lab meetings, informally between trainees and the PI, and at the time of manuscript preparation, when the PI reviews all the raw data files. Morphometric analysis will be performed by blinded teams of students. Inbred C57BL6 strains will be used, with the exception of CF mice for which sibling CF and WT or heterozygous animals will be compared as previously described[78].*

Reviewer Comments:

- *Multiple approaches are used in each aim to more rigorously the hypothesis.*
- *The investigators have multiple steps in the process of the review and analysis of data to ensure validity and to minimize operator biases*
- *The rigor of the scientific approach is outstanding.*

More recently –

***power analyses* have become an expectation!**

Example of Consideration of Biological Variables 2016

"Recent" (2016) example including SABV – New subsection (before Aim 1)

Methods to achieve robust and unbiased results:

… and WT littermate controls were generated as described in Fig. 1. These lines were genotyped and cataloged across 10 backcrosses into the C57BL/6J strain. Only animals that are of the same genetic background and handled in the same way will be compared. Congenic Xxxx KO mice (B6.129P2-Xxxx^{zzzz}/J; stock #xxxx) were obtained from Jackson Laboratories. These mice had been backcrossed with C57BL/6J animals >30 generations. For cultures of dissociated PFC cells obtained from neonates, there is no reason to think that gender differences exist; hence male and female pups will be randomly allocated to experimental groups at P1. For the experiments involving [brain] slices from P30 animals, samples will be prepared from equal numbers of age-matched male and female animals and results will be tracked by gender. Each experiment will be performed in triplicate and repeated at least three times. Dose-response and time-course analyses will be conducted for each compound to ensure that the responses are maximal. We have extensive experience with blinded analysis, treatment paradigms, and group analyses[e.g.50-55]. The Co-Investigator has extensive experience in establishing LTP and LTP-D paradigms in both rats and mice[44,45]. Experimental designs are rigorously vetted including, at a minimum, testing of only a priori hypotheses and blinding for subjective ratings. Except as noted, biological and chemical resources will be obtained from standard commercial suppliers; effects of novel agents are documented in the literature. Data will be analyzed using ANOVA followed by posthoc testing with Student's t-test.

NO

YES

Example of Authentication Attachment 2016

Authentication of Key Biological and/or Chemical Re

Zebrafish:

- Strains: We use zebrafish embryos in our studies controls, as is standard practice in the zebrafish http://zebrafish.org/fish/lineAll.php). Also, all tran strains, and all zebrafish obtained from colleagu ensures that there is no or little variation betwee
- Housing: Zebrafish are housed in a dedicated fis approved by the Association for Accreditation of
- Embryo handling: Embryos are handled using standard protocols described at http://zfin.org/zf_info/zfbook/zfbk.html. All embryos are maintained in egg water, and their general health is inspected daily. Conditions for embryo growth are consistent across experimental dates and researchers.
- Methods to achieve unbiased results: In all experiments, siblings are used as controls, and at least two independent experiments, with a minimum of 6 embryos in each experimental group, are performed. Statistical ana s T-test or ANOVA test

Antibody:
Most antibod made by colleagues a ublish all information tation and protocols for

Examples of what to include:

- *Genetically modified animals*
- *Cultured cells*
- *Antibodies*
- *Assays (e.g. ELISA)*
- *Pharmacological agents*
- *RNA- and DNA-based tools (e.g. primers, siRNAs)*
- *Other*

If not relevant…

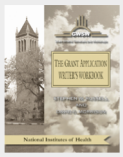
- *Do not ignore*
- *Do not submit blank page*
- *Include form and state that you are not using key biological resources/section is not applicable.*

Topics

NIH National Institutes of Health
Turning Discovery Into Health

Evolution of NIH requirements & scored review criteria

Our recommendations



Other recommendations

Additional examples and other resources

Scored Review Criteria – Significance 2016

1) Does the project address an important problem or a critical barrier to progress in the field?

2) Is there a strong scientific premise for the project?

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Grant Writers' Recommendations – pre 2016, 2016

Research Strategy

a) Significance ***

b) Innovation

c) Approach

- Aim 1
- Aim 2
- Aim 3
- Timeline and Benchmarks for success
- Future Directions

Grant Writers' Recommendations — Approach 2016

Approach

- For each aim
  - Title of Specific Aim
  - Introduction paragraph
  - Research Design paragraphs
    - Experimental design
    - Biological variables
  - Expected Outcomes paragraph
  - Potential Problems …
- Timeline and Benchmarks for success
- Future Directions

Prior to 2016

- Introduction/rationale
- Justification and Feasibility (background + prelim data)
- Research Design
- Expected Outcomes
- Potential Problems and Alternative Strategies paragraph

Grant Writers' Recommendations – Significance 2016

1) **Scientific Premise ***
   - Overall Scientific Premise
   - Scientific Premise of Aim 1 (Literature & Preliminary Results)
   - Scientific Premise of Aim 2 (Literature & Preliminary Results)
   - Scientific Premise of Aim 3 (Literature & Preliminary Results)
2) **Significance of the expected research contribution**

For 3 aims, 4-5 pages

Previously: 0.5-0.75 pp

- *Review of literature; validation of importance of problem*
- *Statement of significance of problem*
- *Discussion of study benefits*

* **The relevant literature:** Strengths and weaknesses

- Rigor of study design (e.g. statistical power, blinded analysis)
- Incorporation of relevant biological variables (e.g. detail regarding sex)

Your preliminary data that contribute to scientific foundation of proposal.

Grant Writers' Recommendations – Approach 2016

Figures in support of hypothesis moved to Significance

Approach

- For each aim
  - Title of Specific Aim
  - Introduction paragraph
  - Research Design paragraphs
    - Experimental design
    - Biological variables
  - Expected Outcomes paragraph
  - Potential Problems …
- Timeline and Benchmarks for success
- Future Directions

Previously

- Introduction/rationale
- Justification and Feasibility (background + prelim data)
- Research Design
- Expected Outcomes
- Potential Problems and Alternative Strategies paragraph

Grant Writers' Recommendations 2016 – Length

Research Strategy

a) Significance (formerly 0.5–0.75 pp → now 4–5 pp)

b) Innovation (formerly 0.5–0.75 pp → still 0.5–0.75 pp)

c) Approach (formerly 10.5–11 pp → now 6.5–7.5 pp)

- Aim 1
- Aim 2
- Aim 3
- Timeline and Benchmarks for success
- Future Directions

Make this fit by including fewer aims???

Recommendations from other NORDP* members (2016)

Query from Stanford:

- *Any feedback on the new scientific premise?*
- *Do you follow the NIH workbook by Stephen W. Russell and David C. Morrison?*
- *Do you have experiences with or strong opinions about the new format?*

Respondent from Duke Medical School:

- *Adhere to Russell and Morrison's guidance generally, but not in this case (length).*
- *New requirements pertain to things researchers should have been doing all along.*
- *Goal is to provide clear, strong message of Significance and Innovation, enabling reviewers to:*
  - *understand the reasoning and check review boxes*
  - *move on to the "good stuff"*
- *Aims to fit Significance into 1.5 pages (3 for projects at interface of multiple areas)*

Respondent from Elsevier:

- *NIH update in 2010 aimed to cut out excess background and keep narrative focused on most relevant context/previous work/importance of project.*
- *New R&R guidance fits perfectly: What is significance of a research project if not "the scientific premise for the proposed project?*

** National Organization of Research Development Professionals*

Recommendations from other NORDP* members (2016)

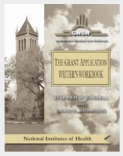
It is not universally accepted that a long Significance section is required for an NIH grant to be good.

Topics

NIH National Institutes of Health
Turning Discovery Into Health

Evolution of NIH requirements & scored review criteria

Our recommendations



Other recommendations

Additional examples and other resources

Examples of Rigor in Applications – posted by NIH

- *Excerpts from awarded applications reviewed under a pilot FOA for rigorous experimental design … this is only one part of updated instruction and review language.*
- *Selected based on high overall impact scores and positive reviewer comments specific to rigor.*
- *Provided to show how elements of rigor and transparency have been succinctly provided in applications; they may not represent all of the aspects/may still have room for improvement.*
- *May be updated as applications are reviewed and awarded under the revised rigor and transparency review.*

Example 1:

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].

Key points:

- *Number of groups, allocation random, age, why that age.*
- *Dosage, number of doses administered*
- *Route of administration, contingency*
- *Group size, power*
- *Blinding, of whom*
- *Experience*

Rigor and Reproducibility | grants.nih.gov
https://grants.nih.gov/reproducibility/index.htm

Examples of Rigor in Applications – posted by NIH

Example 2:

Aim 1: Primary screen: In this high throughput screening assay, we combined the SMN promoter with exons 1-6 and an exon 7 splicing cassette in a single construct that should respond to compounds that increase SMN transcription, exon 7 inclusion, or potentially stabilize the SMN RNA or protein [refs]. The details of the assay and the SMN2-luciferase reporter HEK393 cell line have been extensively validated [refs]. Each point is run in triplicate, the compounds are tested on three separate occasions, and the results are averaged to give an EC50 with standard deviation. Secondary screen: …We analyze SMN protein levels by dose response in quantitative immunoblots with statistical analysis by one-way ANOVA with post-hoc analysis using Dunnett or Bonferroni, as appropriate.

Aim 2: Each set of compounds will include a blinded negative control compound that has been determined to be inactive and that is solubilized in the same manner as test compounds. Mice will be randomly assigned within a litter, and data will be collected and submitted to the PI. For compounds that demonstrate extended survival, the PI will be sure to have these tested in {the collaborators'} labs, and data will be merged and evaluated. To calculate the number of the experimental mice, we will perform an SSD sample size power analysis to ensure that the appropriately minimal number of mice is used in each experimental context. Typically for each compound in life span studies, we will need ~20 SMA animals in the treated group; ~20 SMA animals in the vehicle treated group; ~20 SMA animals in the untreated group. If we can administer the compound in aqueous solution without expedient, the vehicle and untreated groups might be combined, as these should have identical survival. Therefore, no more than 80 SMA animals will be needed per compound.

Key points:

Aim 1
- Brief summary of overall approach
- Number of replicates, same/ different dates, reporting of average with standard deviation
- Types of statistical analysis

Aim 2
- Blinding, solubilization of test and control compounds
- Random assignments
- Who will analyze
- Power analysis; number of animals per group
- Number of animals, contingency

Rigor and Reproducibility | grants.nih.gov
https://grants.nih.gov/reproducibility/index.htm

Examples of Rigor in Applications – posted by NIH

Example 3:

Aim 2: Intensity signal data will be transformed into log values and then modeled by longitudinal methods (reference cited). Specifically, the composite difference in mean intensity signals over time between the bi-specific T cells vs. control groups is assumed to be 2.8 logs with a composite standard deviation of 2.2 logs. Furthermore, we will assume at least five repeated measurements per mouse after T cell infusion and a within-mouse intra-correlation coefficient equal to 0.50. Thus, a sample size of 10 mice per group will provide at least 80% power to detect the above difference between treated versus control group with a 5% significance level. Log-rank test will be used to compare the survival distribution between groups. VAS: Animal numbers are based on the requirement to perform each experiment (power and sample size calculations are described in the Research Strategy), which includes an independent experimental repeat.

Key points, Example 3:
- Methods for conversion of signal data and modeling
- Number of measurements and assumptions made for power analysis
- Statistical measures to be used
- Numbers of animals needed; to be determined independently for each experiment

Example 4:

Aim 1: Statistical considerations: In our preliminary studies consisting of this same cohort of DFUs (n=100) and utilizing 16S rRNA sequencing, we were able to detect dimensions of DFU microbiome, including microbial diversity, that were significantly associated with DFU outcomes. We therefore anticipate that the sample size will provide sufficient power to detect significant differences using metagenomic sequencing, as this is a more sensitive and less-biased assay of microbial identification and diversity.

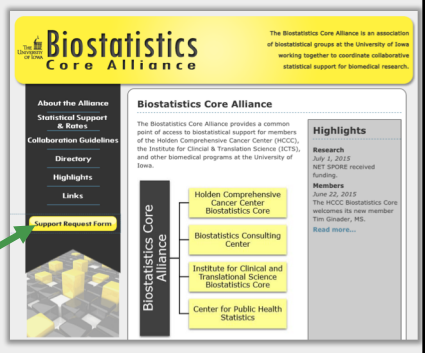
Key points, Example 4:
- Statistical considerations based on preliminary data
- Anticipated power of sample size for new, more sensitive assay
- Statistical measures to be used

Rigor and Reproducibility | grants.nih.gov
https://grants.nih.gov/reproducibility/index.htm

Biostatistics Core Alliance

Partners in offering services to COM faculty, staff, and trainees.

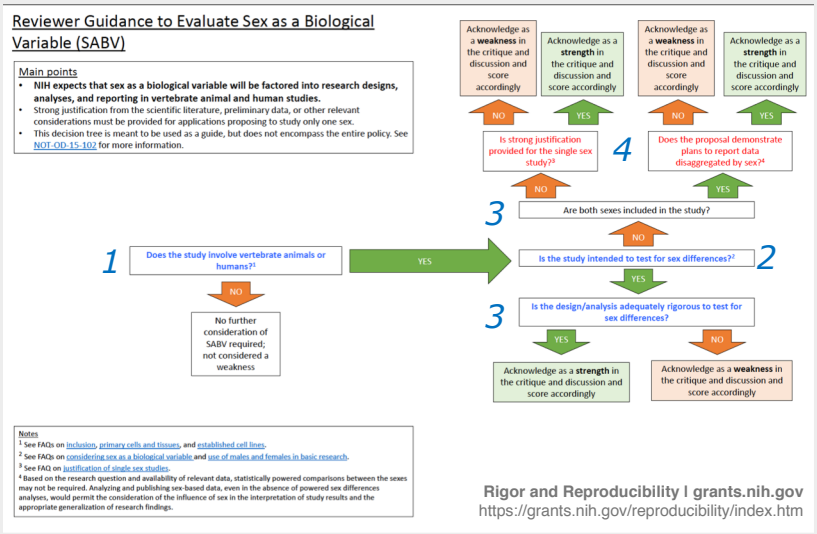
- Center for Public Health Statistics within CoPH
- Biostatistics Consulting Center within CoPH
- Biostatistics, Epidemiology, and Research Design Core (BERD) within ICTS
- Biostatistics Core for HCCC members



Contact staff directly, or for transfer to the most appropriate Center/Core, submit Support Request Form form.

https://bca.public-health.uiowa.edu/

Consideration of Sex as a Biological Variable (SABV)



Rigor and Reproducibility | grants.nih.gov
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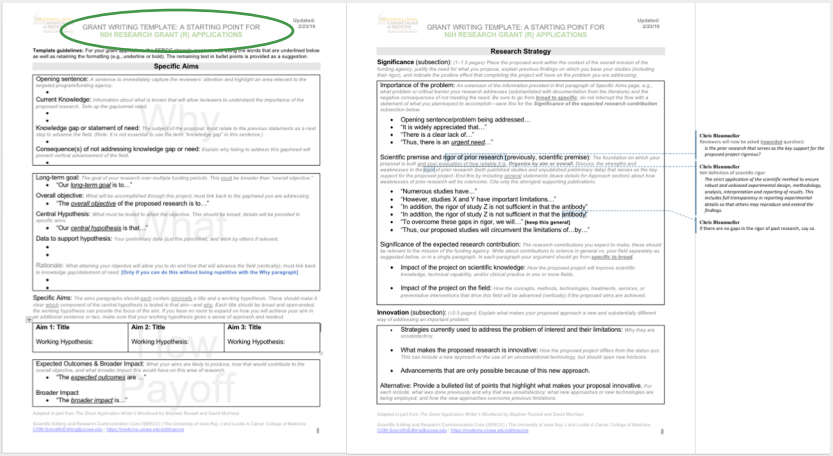
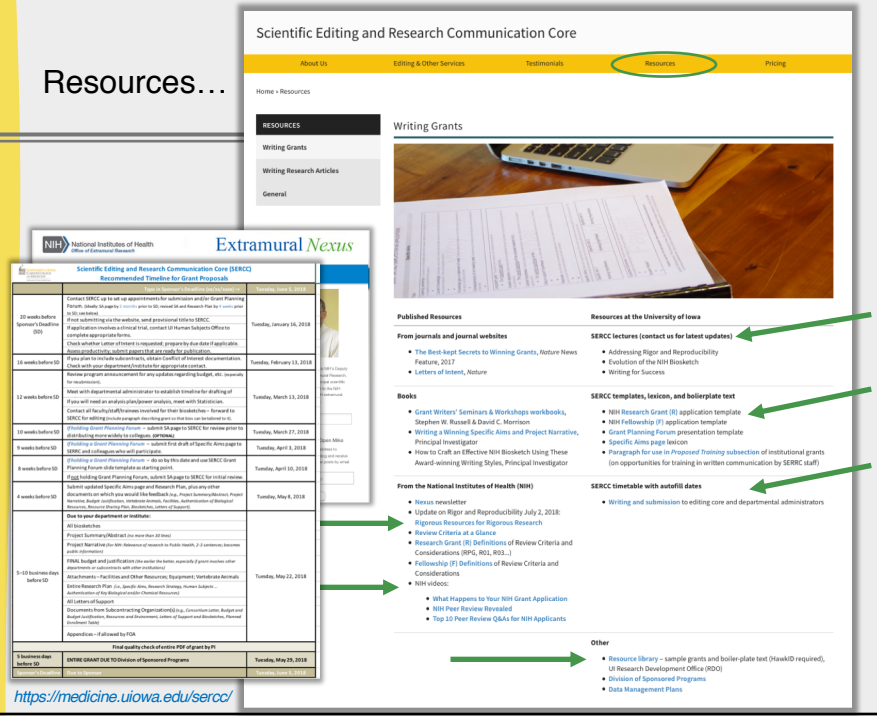
Grant writing template is available…



... will likely change again – will update our Resources web page

Resources…



Grant Resource Library…

Also supports external review of grants

Research Development Office (OVPR)

- Accessible to anyone with a HawkID
- Includes *funded grants*, *boiler-plate text*, etc.

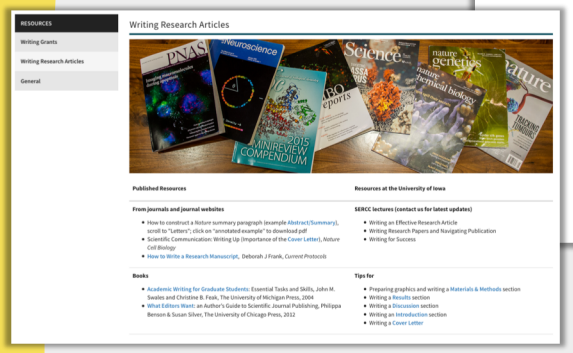
Seeking additional submissions:

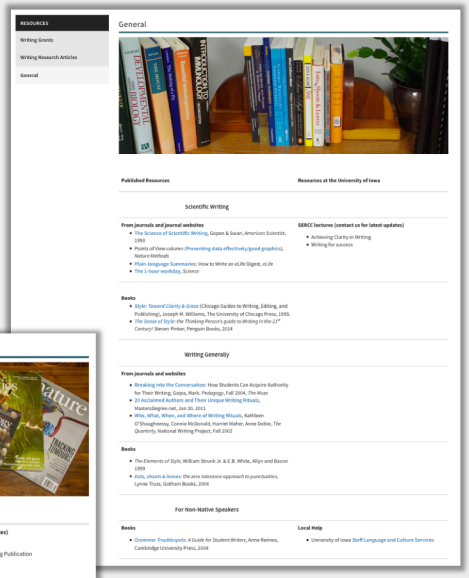
- Applications, in full or in part
  - to any funding agency/foundation (NIH, NSF, MoD, etc.)
  - for any funding mechanism
  - positive and negative reviewer comments
- Recent applications most helpful/older ones also appreciated
- Original or redacted text (assistance available with redaction)

Contact:

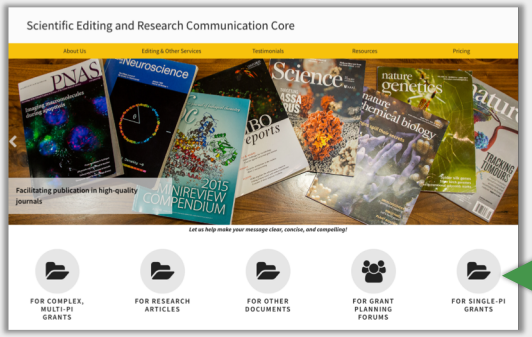
Aaron Kline, Research Development Coordinator
aaron-kline@uiowa.edu

Resources for other writing projects…



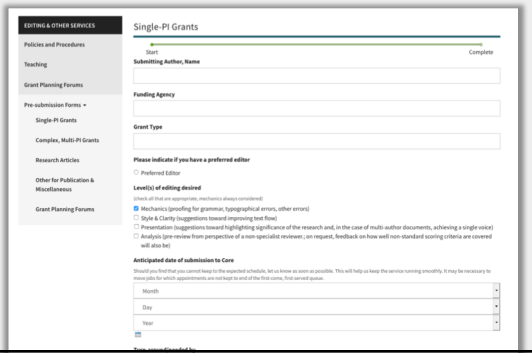


https://medicine.uiowa.edu/sercc/



For help with your projects, contact us early…

…make an appointment for submission



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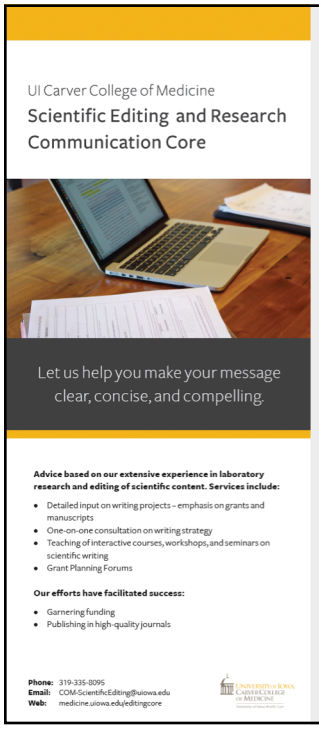


- Detailed input on drafts of writing projects
  - Grant drafts (single- and multi-PI)
  - Research article manuscripts
  - Correspondence to funding agencies and journal offices
  - Other: Review articles, abstracts…
  - Input at following levels:

Mechanics | Style & Clarity | Presentation | Science

☑ ☐ ☐ ☐

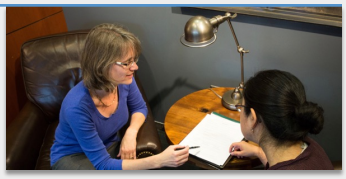
- One-on-one consultation on writing strategy
- Teaching of scientific writing
  - Courses
  - Course lectures
  - Workshops
  - Seminars
- Brainstorming for grants and manuscripts
- Collection and generation of resources
  - Changes in funding agency requirements
  - Grant writing templates (NIH “R” grants, “F” grants)
- Liaising with other RD Professionals at UI, beyond

Questions?

CCOM Scientific Editing and Research Communication Core

Core Director, Scientific Editor & Writing Consultant

Christine M Blaumueller, PhD



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Research Associate Professor
Department of Dermatology

Kris Greiner
Editor, Design Center
Department of Internal Medicine

Our Recommendations – Significance 2016

What is the difference between "scientific premise" and "significance"?

- *The scientific premise will be reviewed as part of the Significance criterion for research grant applications.*
- *Instructions for Significance already include:*
  - *consideration of the importance of the problem or critical barriers to progress*
  - *how the proposed project will improve scientific knowledge*
  - *how the field will change if the aims are achieved*
- *Scientific premise:*
  - *a retrospective consideration of the foundation for the application*
  - *not a prospective analysis should the aims be achieved*

SIGNIFICANCE

Importance of the problem and/or critical barriers to progress

Scientific premise and rigor of prior research

- Numerous studies have…
- However…
- To overcome these gaps in rigor, we will…
- Thus, our proposed studies will circumvent the limitations of… by …

Significance of the expected research contribution

- Impact of the project on scientific knowledge
- Impact of the project on the field

Frequently Asked Questions | Rigor and Transparency
https://grants.nih.gov/reproducibility/faqs.htm#4825

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