Scientific Rigor and Reproducibility

Update on NIH Grant Proposal Requirements

December 8, 2016

Research and Innovation Conference

Jennifer Kemp, PhD
Director, DOM Research Office
Instructor and Medical Writer
Outline

• Rigor and Transparency
  • Why the changes?
  • Scientific Premise
  • Rigorous Experimental Design
  • Relevant Biological Variables
  • Authentication of Resources

Recommendations
Study section experience
Outline

• Rigor and Transparency
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Recommendations

Study section experience
Many publications have noted trouble with lack of reproducibility, transparency when reporting research findings...
The Research Community’s Call for Better Reporting and Reproducibility

How to Make More Published Research True

John P. A. Ioannidis\textsuperscript{1,2,3,4,*}

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

Review Article

Biomolecular Detection and Quantification 2 (2014) 35–42

The reproducibility of biomedical research: Sleepers awake!

Stephen A. Bustin* 

Faculty of Medical Science, Postgraduate Medical Institute, Anglia Ruskin University, Chelmsford CM1 1SQ, UK
Rigor and Transparency: 4 areas of focus

• **Scientific Premise** for the proposed research
• **Rigorous Experimental Design** for robust and unbiased results
• Consideration of **Relevant Biological Variables**
• **Authentication** of key biological and/or chemical resources

Applies to:

Full spectrum of research, from basic to clinical Research, Fellowship, and Training grants

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“Reviewers have asked him to reproduce the experiment.”

What is Scientific Premise?

• Scientific Premise = Research that is used to form the basis for the proposed research questions
• Describe general strengths and weaknesses of prior research that is crucial to support the application
• Could include attention to rigor of previous experimental designs
• Include in Significance section

Premise versus Significance

• Significance:
  Importance of problem
  Barriers to progress
  How project will improve knowledge
  How field will change after project

• Premise:
  Retrospective consideration of the foundation for the application

http://grants.nih.gov/reproducibility/faqs.htm#4825
Suggested structure to address Premise

Within Significance subsection of Research Plan:
Include subheading: “Scientific Premise”
  1-2 paragraphs describing foundation of application
  Discuss current state of knowledge in the area
  Cite appropriately (yours and others)
  Include brief description of your supportive preliminary data
  Describe knowledge gap that your proposal will address
Study section experience with Premise

Premise is a big part of the new requirements
Premise is different from hypothesis, impact, significance
Is the research you propose the logical, best next step, given your and others’ preliminary data?
Reviewers may use this as a reason to be more demanding—must present a better justified application
Reviewers have scored negatively if not enough preliminary data to justify project
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What is Scientific Rigor?

• Experimental design/methods
• Strict application of scientific method to ensure robust and unbiased experimental design, methodology, analysis, etc...
• Includes full transparency in reporting experimental details

Elements of Rigorous Experimental Design

- Appropriate controls
- Replication of experiments
- Randomization
- Blinding
- Sample size/study power
- Statistical methods
- Missing data (plan to address)
- Others as appropriate
Rigor Example

• 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].

http://grants.nih.gov/reproducibility/index.htm
Suggested structure to address Rigor

Within Approach subsection of Research Plan:

• Include subheading(s): “Rigorous Experimental Design”
• Highlight key elements of rigor (which should be woven through your aims)
• Make it easy for reviewers to find and evaluate
Study section experience with Rigor

Proper controls particularly important, describe explicitly
Statistical design particularly important, describe thoroughly
Clinical trials—looking at whether proper exposure variables and outcome variables are used
Much of the info is what has been expected previously, but now it must be packaged a little differently—more explicitly
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“Reviewers have asked him to reproduce the experiment.”

What are Relevant Biological Variables?

- Sex (studies on only one sex must be well justified)
- Age
- Weight
- Underlying health conditions
Suggested structure to address Relevant Biological Variables

Within Approach subsection of Research Plan:

• Include subheading(s): “Consideration of Relevant Biological Variables”

• Explain how variables are factored into experimental design and analysis”
  • Sex, Age, Weight
  • Genetic strain
  • Others as appropriate

• Again, make it easy for reviewers to find and evaluate
Reviewer Guidance to Evaluate Sex as a Biological Variable (SABV)

Main points

- 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.
- This decision tree is meant to be used as a guide, but does not encompass the entire policy. See NOT-OD-15-102 for more information.

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Notes:
1. See FAQs on in vivo, primary cells and tissues, and established cell lines.
2. See FAQs on considering sex as a biological variable and use of males and females in basic research.
3. See FAQ on justification of single sex studies.
4. Based on the research question and availability of relevant data, statistically powered comparisons between the sexes may not be required. Analyzing and publishing sex-based data, even in the absence of powered sex differences analyses, would permit the consideration of the influence of sex in the interpretation of study results and the appropriate generalization of research findings.

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If using both sexes, explain that although the study is not powered to detect sex differences, you will examine male versus female and report those observations.
Study section experience with Relevant Biological Variables

Sex is a critical and commonly discussed issue
State that both male or female will be used, or justify otherwise
State that even if study is not powered to detect sex differences, you will examine and report this
Strain considerations also important
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What is Authentication of Key Biological and/or Chemical Resources?

• Cell lines
• Specialty chemicals
• Antibodies
• Other biologics

Integral to proposed research
Qualities could influence data

New attachment:
“Authentication of Key Biological and/or Chemical Resources”

Describe methods to ensure the identity and validity of key resources

*Do not put preliminary data and other methods in this section

Validation of cell lines very important:

- May include species specific probes
- Mycoplasma specific probes
- Describe how often you will validate
- Mention that you have done this in past, if applicable
Authentication Attachment Guidance

AUTHENTICATION OF KEY BIOLOGICAL AND CHEMICAL RESOURCES (1 page)

All key resources for this proposal will be authenticated to enhance the reproducibility of our results, as appropriate and according to NIH policy.

**Key Biological Resources** that will be utilized in this proposal include:

- **Cell lines**: <list>
- **Transgenic mouse strains**: <list>
- **Antibodies**: <list>
- **Chemicals**: <list>

**Cell lines** will be validated via...<describe methods, including short tandem repeat (STR) analysis or chromosomal analysis as appropriate>

**Transgenic mouse strains** are validated by...<describe techniques for genotyping, etc>

**Antibodies** will be confirmed by...<describe methods such as Western blot, immunoprecipitation, flow cytometry, etc as appropriate>

**Chemicals** will be validated by...<describe methods such as GC or mass spectrometry as appropriate>

Other resources used in this proposal will be standard laboratory reagents. Should we need to generate or obtain additional unique resources in the course of this proposal, they will be authenticated using methods similar to those described above, as appropriate.

**NOTE**: NO additional text or preliminary data; do NOT circumvent page limits of your 12 page research plan. Methods for authentication will vary and should be based on accepted methods appropriate for the particular field of research. This template was developed by the Department of Medicine Research Office.
Cell line validation method:
STR analysis
rapid, inexpensive
### Summary of NIH Rigor Requirements

<table>
<thead>
<tr>
<th>Where to address?</th>
<th>Scientific Premise</th>
<th>Rigorous Experimental Design</th>
<th>Relevant Biological Variables</th>
<th>Authentication of Key Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scored?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No, but...</td>
</tr>
</tbody>
</table>

Significance: New Attachment
Summary of Feedback and Recommendations

• Many study sections taking this very seriously
• Reviewers are specifically instructed to address new elements (Premise, Rigor, Variables) in Overall Impact paragraph at beginning of their individual reviews
• First cycle may have been less strictly reviewed; expected to be more serious in future
• Premise—describe explicitly, heavily scrutinized
• Rigor—focus on proper controls and rigorous methods
• Relevant variables—sex very important
• Authentication—cell line validation very important
Rigor and Reproducibility

Enhancing reproducibility through rigor and transparency: the information provided on this website is designed to assist the extramural community in addressing rigor and reproducibility in grant applications due on January 25, 2016, and beyond.

On This Page:
- Goals
- News
- Guidance: Rigor and Reproducibility in Grant Applications
- Timeline
- Resources
- Stakeholder Input
- Previous Events
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Goals
Open Mike

Helping connect you with the NIH perspective, and helping connect us with yours

Posted on January 28, 2016 by Mike Lauer

Scientific Premise in NIH Grant Applications

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. This post is the first in a series addressing each of these four areas, starting with scientific premise.
Summary of Upcoming NIH Changes

• Appendix Policy:
  • Eliminates most appendix material
  • Papers and manuscripts no longer acceptable
  • May include clinical trial protocols, blank informed consent forms, blank data collection instruments, other items specified in FOA

• Post-Submission Materials Policy
  • Simplified policy on types of materials allowable

• Clinical Trial Policies
  • Clinical trial applications must be in response to specific FOAs
  • Must contain elements such as protocol information
  • New plan to disseminate results should be included

NOT-OD-16-129 appendix policy change
NOT-OD-16-130 post-submission materials
Toward a New Era of Trust and Transparency in Clinical Trials

Clinical trials are the most publicly visible component of the biomedical research enterprise, from the potential human application of novel laboratory findings to the generation of robust evidence about treatments or preventive interventions in routine clinical care. These trials are also the point at which biomedical research most directly engages human participants—dedicated volunteers who trust investigators to uphold the highest standards of scientific rigor and ethical oversight. While clinical trials have evolved and improved over time—producing impressive advances in diagnosis, treatment, and prevention—there are still major challenges. Therefore, fundamental changes are needed to reflect science and society’s movement to increased efficiency. The aim is to help ensure that all involved in the clinical trial enterprise have the appropriate knowledge about the design, conduct, monitoring, recording, analysis, and reporting of clinical trials. While GCP training on its own may not be sufficient, it provides a consistent high-quality standard.

Another important change at the beginning of the clinical trial lifecycle is a new NIH policy that will require all applications for clinical trials to be submitted in response to clinical trial–specific Funding Opportunity Announcements (FOAs). This will mean that applications including one or more clinical trials will no longer be accepted in response to parent funding announcements, which are broad FOAs that allow researchers to submit.
Thank you!

Please provide feedback and share your experiences during upcoming peer review

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Resources Available

Grant Writing Assistance
Proposal development, writing, and editing support

DOM Research Funding Programs
Grants from the DOM supporting innovative research

Application Tools & Resources
Tools and templates to streamline grant application processes

Management of Research Space
Requests for additional research, storage or office space

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