Update: New NIH Requirements for 2016 Grant Proposals

What are they and how do I get it right?

21 March 2016

Jennifer Kemp, PhD
Instructor and Medical Writer
Outline

• Overview of upcoming NIH changes for 2016
• Rigor and Transparency
• Vertebrate Animals
• Biosketch clarifications
• Summary of other changes
Outline

• Overview of upcoming NIH changes for 2016
• Rigor and Transparency
• Vertebrate Animals
• Biosketch clarifications
• Summary of other changes
Overview:
Timeline of recent and upcoming changes

New Biosketch Format
5 pages
Scientific accomplishments
Link to publication list

Phase 1
- Rigor and Transparency
- Vertebrate Animals
- Definition of Child (under 18 yrs)
- Research Training
- Others

Phase 2
- Switch to application FORMS-D
- Phase 1 changes extended to T and F series
  (Rigor, Vertebrate Animals)
- Inclusion forms
- Research training (additional changes)
- Appendix policy
- New font guidelines
- Biosketch clarifications
- Others

May 25, 2015
January 25, 2016
May 25, 2016

See NOT-OD-15-032, December 5, 2015 (new biosketch)
and NOT-OD-16-004, October 13, 2015 (summary of 2016 changes)
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“Reviewers have asked him to reproduce the experiment.”

The Research Community’s Call for Better Reporting and Reproducibility

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

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

Florian Prinz, Thomas Schlange and Khursru 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
NIH plans to enhance reproducibility

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring. As leaders of the US National Institutes of Health (NIH), we share this concern and here explore some of the significant interventions that we are planning.

Science has long been regarded as ‘self-correcting’, given that it is founded on the replication of earlier work. Over the long term, that principle remains true. In the shorter term, however, the checks and balances that once ensured scientific fidelity have been hobbled. This has compromised the ability of today’s researchers to reproduce others’ findings.

Let’s be clear: with rare exceptions, we have no evidence to suggest that irreproducibility is caused by scientific misconduct. In 2011, the Office of Research Integrity of the US Department of Health and Human Services pursued only 12 such cases. Even if this represents only a fraction of the actual problem, fraudulent papers are vastly
Rigor and Transparency: new requirements

• 4 new areas of focus
• New instructions for Research Strategy
• New attachment: “Authentication of Key Biological and/or Chemical Resources”
• New review criteria

See NOT-OD-16-011 and NOT-OD-16-012
Rigor and Transparency: 4 areas of focus

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

This applies to the **full spectrum** of research, from basic to clinical.

*activity code exceptions can be found in the notice*

Rigor and Transparency: New Instructions for Research Strategy

• **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.”

• **Approach**: “Describe the experimental design and methods proposed and how they will achieve robust and unbiased results.”

• **Approach**: “Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans....”

See NOT-OD-16-011, NOT-OD-15-102
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...”

http://grants.nih.gov/reproducibility/index.htm
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
  Include brief description of your preliminary data (strengths)
  Describe knowledge gap that your proposal will address
What is Scientific Rigor?

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

http://grants.nih.gov/reproducibility/index.htm
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 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].

http://grants.nih.gov/reproducibility/index.htm
Rigor Example 2a

• 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.

http://grants.nih.gov/reproducibility/index.htm
Rigor Example 2b

- **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.

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 may be woven through your aims)
- Make it easy for reviewers to find and evaluate
What are Relevant Biological Variables?

• Sex (studies on only one sex must be well justified)
• Age
• Weight
• Underlying health conditions

• How to address? Again, make it easy for reviewers...
• Subsection in Research Plan: “Consideration of Relevant Biological Variables”
What is Authentication of Key Biological and/or Chemical Resources?

- Cell lines
- Specialty chemicals
- Antibodies
- Other biologics

- May differ from lab to lab or over time
- Qualities that could influence research data
- Integral to proposed research

http://grants.nih.gov/reproducibility/index.htm
New Attachment: Authentication

“Authentication of Key Biological and/or Chemical Resources”

Describe methods to ensure the identity and validity of key biological and/or chemical resources (may include cell lines, specialty chemicals, antibodies, other biologics).

Do not put preliminary data and other methods in this section

See NOT-OD-16-011
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:** xxxxx
- **Transgenic mouse strains:** xxxxxx
- **Antibodies:** xxxxx

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

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

**Antibodies** will be confirmed by...<describe methods>

All other antibodies and reagents we anticipate using for the proposed work are commercially available and validated by the companies that provide them. 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.
Fixing problems with cell lines
Technologies and policies can improve authentication

Despite the important role of cell culture in the study of biology and medicine, evidence has accumulated that cell lines are frequently misidentified or contaminated by other cells or microorganisms. This can be a substantial problem in many fields, such as cancer research, where drugs are initially tested using a cell line derived from the targeted type of tumor (1). If a drug is tested on the wrong cell line, research can lead to unreliable results, and discovery of effective treatments can be delayed. Even in basic research, use of mistaken cell lines can hinder progress because of variations in cell behavior among different cell types. Given these concerns, developing corrective measures for cell line misidentification and contamination warrants renewed attention.

Since the 1960s, more than 400 widely used cell lines worldwide have been shown to have been misidentified (2, 3). Cells originally thought to have been derived from one tissue type have later been found to be from a different tissue. In some cases, even the species of the cells has been misidentified. A 2013 study of 122 different head and neck cancer cell lines revealed that 57 (39%) were misidentified (4). Analysis of a variety of tissue culture collections and cells sent to repositories for corroboration and storage from labs in the United States, Europe, and Asia suggest that at least 15% of cell lines are misidentified or contaminated (4–5).

Misidentified cell lines can create problems at many levels of biomedical research. For example, studies using just two misidentified cell lines were included in three grants funded by the U.S. National Institute of Health (NIH), two clinical trials, 11 patents, and >100 papers (5). Nonetheless, the need for validation and accurate reporting of cell line identity does not appear to be widely recognized by researchers; a 2013 study found that fewer than half of cell lines were unambiguously identified in published studies (7).

A number of factors contribute to the problems of cell line misidentification and contamination. For example, inadvertently using a pipette more than once can introduce contaminants. If the contaminating cell line divides more rapidly than the original cells, it can quickly dominate the population, changing the identity of the culture. This event often goes undetected because cells from other
Cell line validation

• One method uses short tandem repeat analysis (STR)
• Rapid, inexpensive, can use online databases to compare STR fingerprints to verify cell line identity for common human cell lines

• Barbara Davis Center core facility provides cell line authentication services using Promega kit with 16 STR loci
• Investigator provides DNA or cells, receives results in ~1 week.
• Cost is $65 per sample, or $120 with match analysis
• Contact Randy Wong (Randall.wong@ucdenver.edu) for information
OMG! They're HeLa Cells!

Make sure you are working with the right human cell line. Authenticate!

- NIH is expecting authentication for 2016 applications. For grant applications due on January 25, 2016 and beyond, grantees will be required to authenticate key biological resources, including cell lines.
- More and more journals are requiring cell line authentication prior to publication. e.g., AACR strongly encourages the authentication of cell lines used in the research reported in its journals. AACR Journals: Instructions to Authors.

Learn More About the BDC BioResources Core Facility's Cell Line Authentication Service. Contact:

Randy Wong
303.724.6825
randall.wong@ucdenver.edu
Rigor and Transparency: New Scored Review Criteria

• **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?”

• **Approach**: “Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?”

See NOT-OD-16-011
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.”

See NOT-OD-16-011
# Summary of 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
- Approach
- Approach
- New Attachment
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
- References

http://grants.nih.gov/reproducibility/index.htm
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“At first I was happy I made smart transgenic mice.”

Smart mice cartoon source: http://vadlo.com/cartoons.php?id=42
Simplification of Vertebrate Animals Section

Changes remove redundancy with IACUC review

Things you DO still need:

- **Description of procedures** (species, strains, ages, sex, total numbers)
- **Justifications** (appropriateness of species for proposed research)
- **Minimization of pain and distress** (describe interventions to minimize)
- **Euthanasia** (state whether consistent with AVMA guidelines)

Things you NO LONGER need:

- Description of *veterinary care*
- Justification for the *number of animals*
- A description and justification of the **method of euthanasia** is required only if the method is not consistent with AVMA Guidelines

See NOT-OD-16-006
Outline

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New Biosketch Format (May 25, 2015)

- 5 page limit (increased from 4)
- Scientific accomplishments (describe up to 5)
- Link to publications

B. Positions and Honors

Positions and Employment

1999-2000: Fellow, Division of behavioral Alcoholism, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD
2001-2004: Postdoctoral Fellow, Department of Psychology, University of Maryland, College Park, MD
2004-2007: Assistant Professor, Department of Psychology, University of Washington, Seattle, WA
2007-2013: Associate Professor, Department of Psychology, University of Washington, Seattle, WA
2013-2015: Professor, Department of Psychology, University of Washington, Seattle, WA

See NOT-OD-15-032

A. Personal Statement

I have the expertise, leadership, teaching, experience and motivation necessary to successfully carry out the proposed research project. I have a demonstrated track record in psychology, with specific training and expertise in etiological and survey research and design. My expertise includes laboratory psychology, aspects of drug addiction, and community health. I have had the opportunity to work with several universities and non-profit organizations that have helped to support the proposed research by developing effective measures of substance use, cognition, and other psychological factors relevant to the aging substance abuser and the cognitive impairments that will make it possible to conduct and track early and late life changes as developed in this study.

In addition, I have been a principal investigator on several grants, including the National Institute on Drug Abuse, the National Institute on Aging, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Mental Health, and the National Institute of Child Health and Human Development. These grants have allowed me to conduct research on the determinants of drug use and the factors that contribute to the development and maintenance of drug use disorders in later life.

My recent work has focused on the development of new methods for assessing the effects of substance use on cognition and aging, and the development of new interventions to prevent and treat substance use disorders in older adults. My research has been funded by the National Institute on Aging, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism.

C. Contribution to Sciences

1. My early work has clearly addressed the link between substance use and cognitive decline in older adults. However, there is a need for further research to understand how increased rates of substance use and abuse are associated with cognitive decline in older adults. This is particularly important because the aging population is growing and the need for effective interventions to prevent and treat substance use disorders is critical.

2. My recent work has focused on the development of new methods for assessing the effects of substance use on cognition and aging, and the development of new interventions to prevent and treat substance use disorders in older adults. My research has been funded by the National Institute on Aging, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism.

D. Research Support

Opening Research Support

R21DA032731 (01/01/2015-12/31/2018)

Health interventions and behavioral interventions among older substance abusers

The goal of this study is to compare the effects of substance abuse interventions on health outcomes in an urban population of older substance abusers. Role: PI

R21AA020375 (01/01/2015-12/31/2018)

Physical disabilities, depression and substance abuse in the elderly

The goal of this study is to identify depressive symptoms and depression-related factors affecting substance abuse in an urban population of older substance abusers. Role: Co-Investigator

Competing Research Support

R21AA135337 (01/01/2015-12/31/2018)

Competitive research support for behavioral interventions in substance abuse in older adults

The goal of this study is to develop a community-based intervention for reducing alcohol use among older adults. Role: PI

See NOT-OD-15-032
Biosketch Clarifications

• A URL for a publication list is optional and must be to a government website (.gov) like My Bibliography
• Allowing publications and research products to be cited in both the personal statement and the contributions to science sections
• Graphics, figures and tables are not allowed

See NOT-OD-16-004
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Effective for January 25, 2016 due dates:

• **Definition of Child** = under 18 years old (previously under 21)

• **Research Training**: updated instructions
Effective for May 25, 2016 due dates:

• Use new FORMS-D application forms

• **Rigor and Transparency, Vertebrate Animals Changes extended** to institutional training and individual fellowship applications

• **Research Training**: new table format

• **Inclusion Forms**: new Inclusion Enrollment Report form replaces old Planned and Cumulative Inclusion Enrollment Reports

• **New PHS Assignment Request Form**: Specify NIH institute preference, study section, reviewers in conflict, expertise needed to review.

• **New Fonts**: additional fonts allowed

• **Appendix Policy**: changes to be announced spring 2016

See NOT-OD-16-004
Thank you!

Please provide feedback and share your experiences during upcoming peer review

Jennifer.T.Kemp@ucdenver.edu
Contacts

Sean Colgan, PhD
Vice Chair for Basic Research
Sean.Colgan@ucdenver.edu
303-724-7235

Marc Moss, MD
Vice Chair for Clinical Research
Marc.Moss@ucdenver.edu
303-724-6074

Chris Brands
Grants Manager
Chris.Brands@ucdenver.edu
303-724-5952

Sheryl Hartmann
Grants Coordinator
Sheryl.Hartmann@ucdenver.edu
303-724-1786

Jennifer Kemp, PhD
Grant Writer
Jennifer.T.Kemp@ucdenver.edu
303-724-9546

Resources Available

Grant Writing Assistance
Proposal development, writing, and editing support

DOM Research Funding Programs
Grants from the DOM supporting innovative research

Divisional Grant Support
Pre- and post-award support augmenting divisional grant management

Clinical Research Support
Key resources and access to DOM-specific regulatory assistance

Research Development
Identification and targeting of funding sources beyond the NIH

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

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

medschool.ucdenver.edu/DOMResearch
DOMResearch@ucdenver.edu