Scientific Rigor and Reproducibility

Update on NIH Grant Proposal Requirements

December 8, 2016

Research and Innovation Conference

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Outline

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

Recommendations

Study section experience

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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

PLOS Medicine | www.plosmedicine.org

October 2014 | Volume 11 | Issue 10 | e1001747

John P. A. Ioannidis[1,2,3,4]*

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

NATURE REVIEWS | DRUG DISCOVERY

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

Nature Announces Reproducibility Initiative

The journal is sharpening its review of life science papers and giving authors additional space to document more detailed methods.

By Kate Yandell | April 25, 2013

Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an alarming degree, it is not

Oct 19th 2013 | From the print edition Timekeeper Like 22k Tweet

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

See NOT-OD-16-011 and http://grants.nih.gov/reproducibility/index.htm

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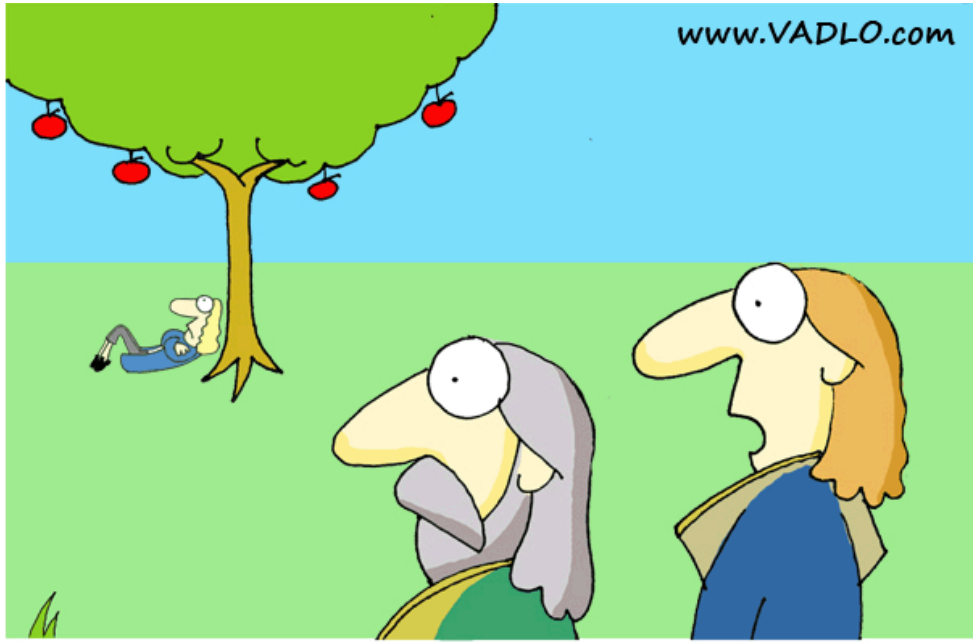

"Reviewers have asked him to reproduce the experiment."

Newton cartoon source: http://vadlo.com/cartoons.php?id=2

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

NOT-OD-16-011, NOT-OD-15-102, 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
- Cite appropriately (yours and others)
- Include brief description of <u>your</u> 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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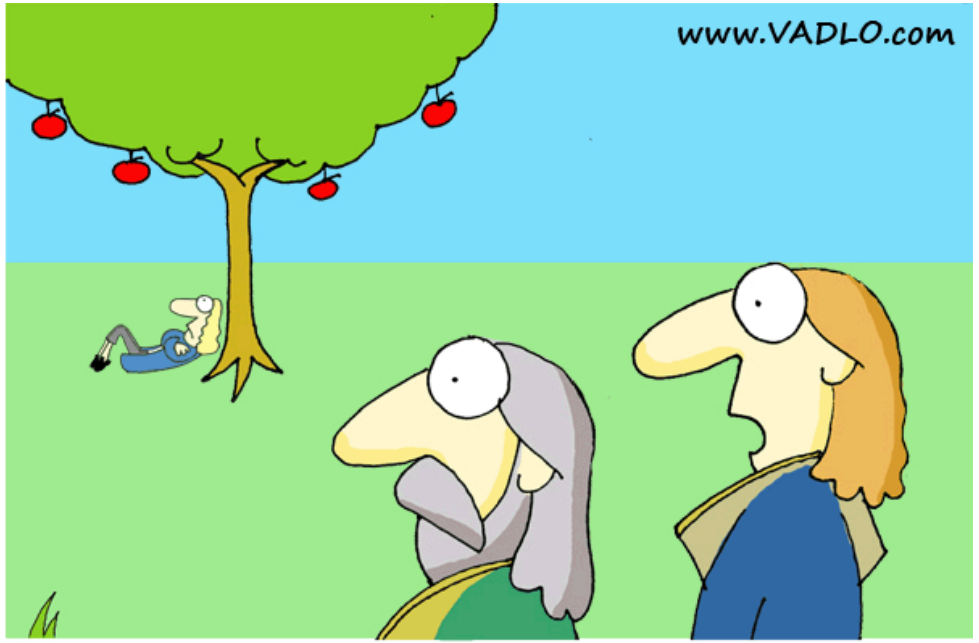

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What is Scientific Rigor?

- 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

NOT-OD-16-011, NOT-OD-15-102, 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

- 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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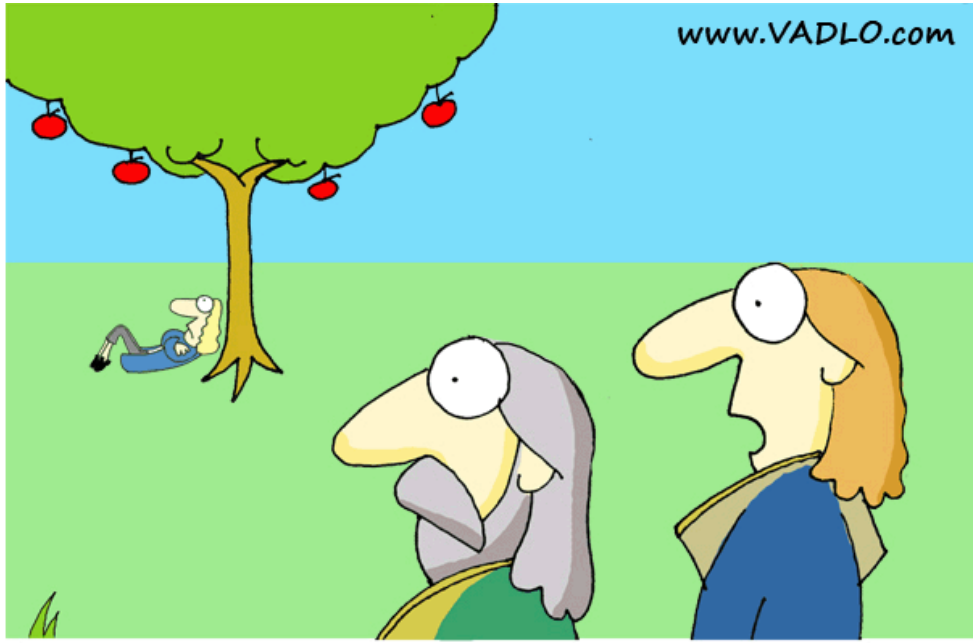

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What are Relevant Biological Variables?

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

Suggested structure to address Relevant Biological Variables

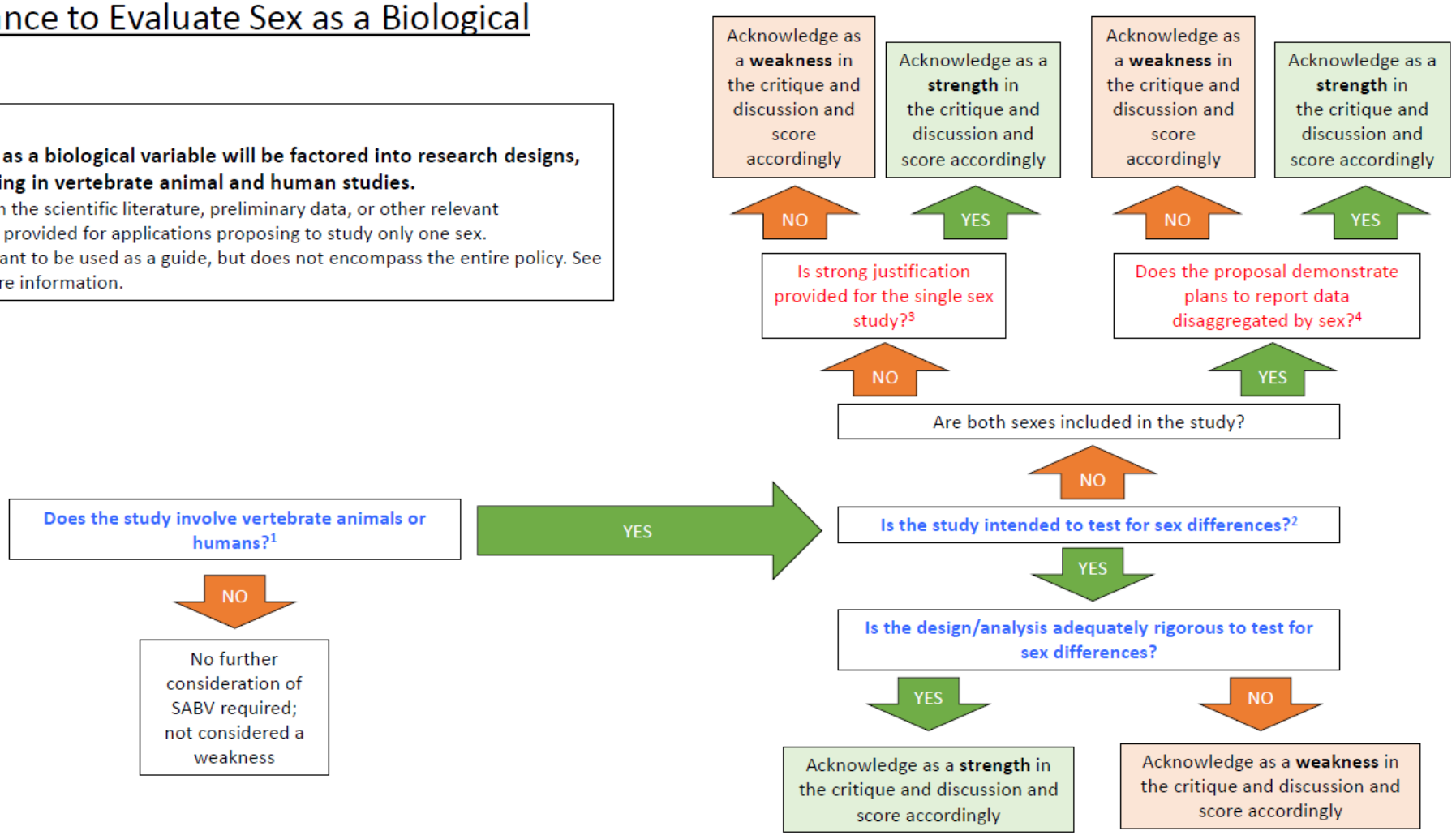
Within Approach subsection of Research Plan:

- 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.



Notes

[1] See FAQs on inclusion, 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.

https://grants.nih.gov/grants/peer/guidelines_general/SABV_Decision_Tree_for_Reviewers.pdf

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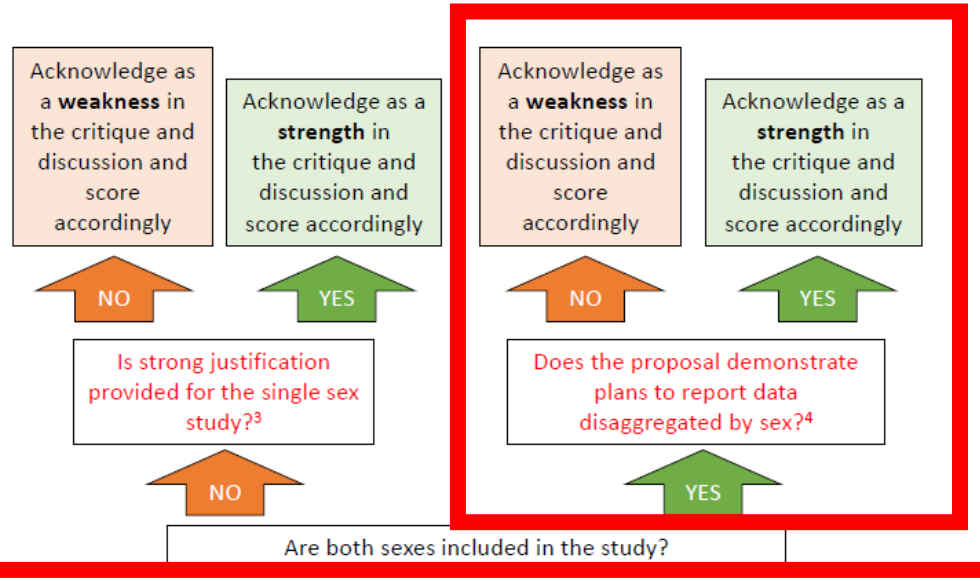

If using both sexes, explain that although the study is not powered to detect sex differences, you will examine male versus female and report those observations.

https://grants.nih.gov/grants/peer/guidelines_general/SABV_Decision_Tree_for_Reviewers.pdf

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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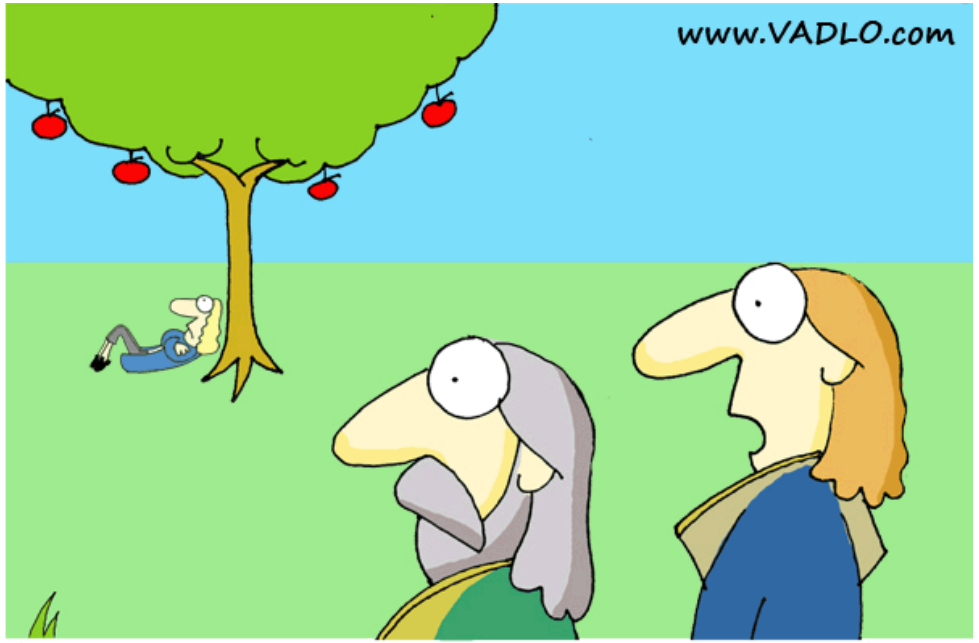

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What is Authentication of Key Biological and/or Chemical Resources?

- 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*

NOT-OD-16-011 and http://grants.nih.gov/reproducibility/index.htm

Study section experience with Authentication Attachment

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>

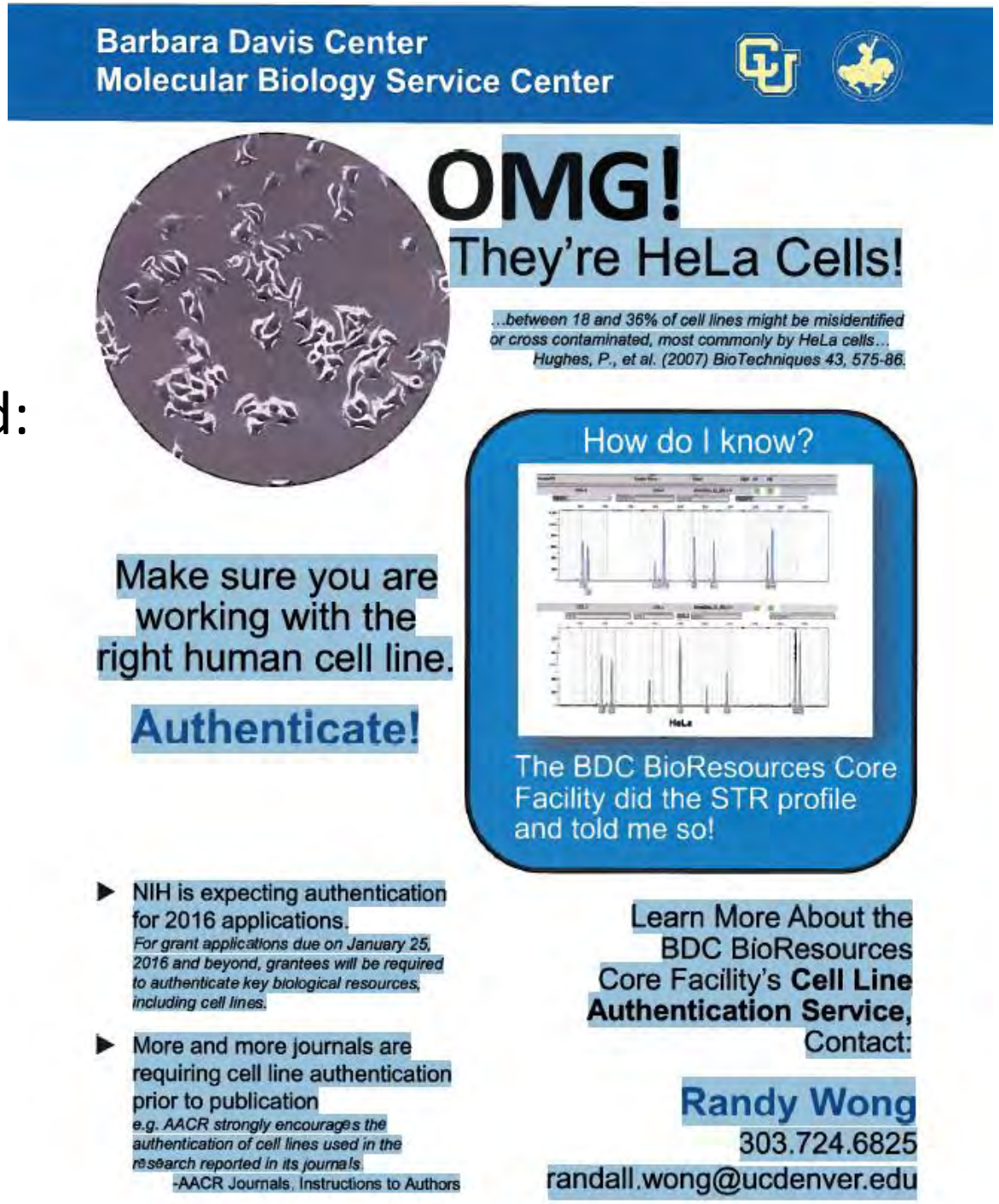
Antibodies will be confirmed by…<describe methods such as Western blot, immunoprecipitation, flow cytometry, etc as appropriate>

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

	Scientific Premise	Rigorous Experimental Design	Relevant Biological Variables	Authentication of Key Resources
Where to address?	Significance	Approach	Approach	New Attachment
Scored?	Yes	Yes	Yes	No, but…

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

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

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.

Dr. Michael Lauer is NIH's Deputy Director for Extramural Research, serving as the principal scientific leader and advisor to the NIH Director on the NIH extramural research program.

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

JAMA®

VIEWPOINT

Toward a New Era of Trust and Transparency in Clinical Trials

Kathy L. Hudson, PhD
National Institutes of Health, Bethesda, Maryland.

Michael S. Lauer, MD
National Institutes of Health, Bethesda, Maryland.

Francis S. Collins, MD, PhD
National Institutes of Health, Bethesda, Maryland.

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 increase 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 and 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

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