21st Century Cures Act Update: Research Rigor and Reproducibility

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Deputy Director for Extramural Research
National Institutes of Health

Meeting of the Advisory Committee to the Director (ACD)
National Institutes of Health
Building 31, 6th Floor Conference Room 6C
Bethesda, Maryland
December 14-15, 2017
Disclosures: None
ACD Working Group

• ACD
  – Russ Altman (Chair)
  – Mary Sue Coleman
  – Lisa Cooper
  – Jose Florez
  – Linda Griffith
  – Peter MacLeish

• NIH
  – Michael Lauer
  – Pritty Joshi
  – Jennifer Plank-Bazinet
  – Patricia Valdez
Section 2039 requires the NIH Director to convene a working group under the ACD to develop and issue recommendations through the ACD for a formal policy, which may incorporate or be informed by relevant existing and ongoing activities, to enhance rigor and reproducibility of scientific research funded by NIH.
<table>
<thead>
<tr>
<th>Element of Rigor</th>
<th>Section of Application</th>
<th>Criterion Score</th>
<th>Additional Review Consideration</th>
<th>Contribute to Overall Impact?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Premise</td>
<td>Significance</td>
<td>NA</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Scientific Rigor</td>
<td>Approach</td>
<td>NA</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Consideration of Relevant Biological Variables Such as Sex</td>
<td>Approach</td>
<td>NA</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Authentication of Key Biological and/or Chemical Resources</td>
<td>New Attachment</td>
<td>NA</td>
<td>Adequate or Inadequate</td>
<td>No</td>
</tr>
</tbody>
</table>

January 2016
Timeline for ACD WG

- **21st Century Cures Act**
- **First meeting of the ACD WG**
- **Prelim report to full ACD**
- **Present options to the full ACD**
- **Final Report from the ACD WG (TBD)**
- **NIH action on ACD WG recs (TBD)**
- **NIH report to Congress**

- **2017**
  - May 25, 2017
  - June 8-9, 2017
  - Dec 14-15, 2017

- **2018**
  - TBD (before Dec 2018)
  - TBD (before June 2018)
### Interim Recommendations

**Application**
- Highlight what’s important
- Section(s) for rigor
- Not just authentication
- “CONSORT-like” checklist
- Clarifies review priorities

**Resources**
- Validated, vetted materials

<table>
<thead>
<tr>
<th>Component</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial design</td>
<td>3a, 3b</td>
</tr>
<tr>
<td>Participants</td>
<td>4a, 4b</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a, 6b</td>
</tr>
<tr>
<td>Sample size</td>
<td>7a, 7b</td>
</tr>
<tr>
<td>Randomisation:</td>
<td>8a, 8b</td>
</tr>
<tr>
<td>Sequence generation</td>
<td></td>
</tr>
<tr>
<td>Allocation</td>
<td>9</td>
</tr>
<tr>
<td>Concealment mechanism</td>
<td></td>
</tr>
<tr>
<td>Implementation</td>
<td>10</td>
</tr>
<tr>
<td>Blinding</td>
<td>11a</td>
</tr>
</tbody>
</table>

Options to Consider: Start with PHS 398

<table>
<thead>
<tr>
<th>Introduction</th>
<th>Research Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Research Strategy = 12 pages</td>
</tr>
<tr>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>Vert animals</td>
<td>Select agent</td>
</tr>
<tr>
<td>MPI</td>
<td>Authentication</td>
</tr>
<tr>
<td>Appendix</td>
<td></td>
</tr>
</tbody>
</table>
**Option 1: New Attachment in Research Plan**

Add section 5 here

Include **one document** with description of premise, rigor, and biological variables.
<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Draws attention</td>
<td>• Duplicate information entry</td>
</tr>
<tr>
<td>• Located in one place</td>
<td>• Free-form may miss key items</td>
</tr>
<tr>
<td>• With Research Plan</td>
<td>• More content for review</td>
</tr>
<tr>
<td>• More space</td>
<td>• OMB clearance</td>
</tr>
<tr>
<td>• Contribute to score*</td>
<td></td>
</tr>
</tbody>
</table>

*Authentication Plan does not contribute to score
Option 2: New Headings in Research Strategy

Include headings with descriptions of premise, rigor, and biological variables
## Option 2 Considerations

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Draws attention</td>
<td>• Duplicate information entry</td>
</tr>
<tr>
<td>• All in one location</td>
<td>• Free-form may miss key items</td>
</tr>
<tr>
<td>• With Research Plan</td>
<td>• Collision with page limits</td>
</tr>
<tr>
<td>• Neutral for review content</td>
<td></td>
</tr>
<tr>
<td>• No need for OMB clearance</td>
<td></td>
</tr>
<tr>
<td>• Contribute to score*</td>
<td></td>
</tr>
</tbody>
</table>

*Authentication Plan does not contribute to score*
### Option 3: New Form

**Scientific Premise**
Describe the scientific premise for the proposed project.

**Scientific Rigor**
- Inclusion, Exclusion
- Allocation
- Blinding
- Sample Size
- Analysis Plans

**Biological Variables**
Consideration of biological variables such as sex

Fill-in or attachment

Include **detailed, separate documents** on premise, rigor, and biological variables.
Collect granular information for scientific rigor.
## Option 3 Considerations

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Draws attention</td>
<td>• Disconnect from Research Plan</td>
</tr>
<tr>
<td>• Specificity of items</td>
<td>• Duplicate information entry</td>
</tr>
<tr>
<td>• Mix discrete and text</td>
<td>• More content for review</td>
</tr>
<tr>
<td>• Easier to mine data</td>
<td>• Other rigor items?</td>
</tr>
<tr>
<td>• More space</td>
<td>• OMB clearance</td>
</tr>
<tr>
<td>• Contribute to score*</td>
<td></td>
</tr>
</tbody>
</table>

*Authentication Plan does not contribute to score*
Resource Validation: There’s a Market

Antibody Validation Database

enter the target name

Search examples: H3K9me3, H3K27me3, H3K4me3

71 targets 261 antibodies 4 species 14 sources 19 validators 1 project


https://www.proteinatlas.org
http://compbio.med.harvard.edu/antibodies/
Solving The Reproducibility Crisis

Were you ever frustrated by not being able to reproduce experiments published by other labs, or for that matter, from your own lab? If so, you are not alone; we all face this looming "reproducibility crisis" in biomedical research.

What is the reproducibility crisis?

There is a recent outpouring of concern among the scientific community about the validity of many published results. Recent findings suggest that ~50% of published literature is not reproducible, with a cost of ~38 billion dollars annually in the US alone.1

Apart from wasted time and money, invalidated research diminishes public trust, and hinders the progress of science. These alarming facts prompted serious introspection and discussions among scientists, universities and industry partners to identify the core causative factors and develop best practices to avert the situation.

Novel Antibody Scoring System Enters Alpha Testing

https://www.benchsci.com/reproducibility/
A Kind of Consumer Reports?

https://www.bioz.com
Interim Recommendations on Training

• Training
  – Ongoing funded projects (PA-16-060)
  – Incorporate into spectrum of ethics training
  – NAS: “detrimental research practices”

https://www.nap.edu/catalog/21896/fostering-integrity-in-research
NIGMS Predoctoral T32 Pilot

National Institute of General Medical Sciences Ruth L. Kirschstein National Research Service Award (NRSA) Predoctoral Institutional Research Training Grant (T32)

• PAR-17-341
• Published October 6, 2017
• First application due date May 25, 2018
• Earliest start date July 2019

• A strong foundation in scientific reasoning, rigorous research design, experimental methods, quantitative approaches, as well as data analysis and interpretation; …

• A commitment to approaching and conducting biomedical research **responsibly and with integrity**;

• Experience initiating, conducting, interpreting, and presenting rigorous and reproducible biomedical research with increasing self-direction …

Assessment of Mentors Includes …

- Record of rigorous research;
- Sufficient time commitment for training;
- Plans to ensure trainees develop skills in experimental design, methods of data collection, analysis, interpretation, and reporting
- Trainees conducted rigorous research

• Research application:
  – How granular?
  – Separate or included in research plan?
  – How to avoid duplicate information?

• Validation resources out there…

• Research training:
  – How best to integrate rigor with responsible conduct?