

21st Century Cures Act Update: Research Rigor and Reproducibility

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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

- 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.**



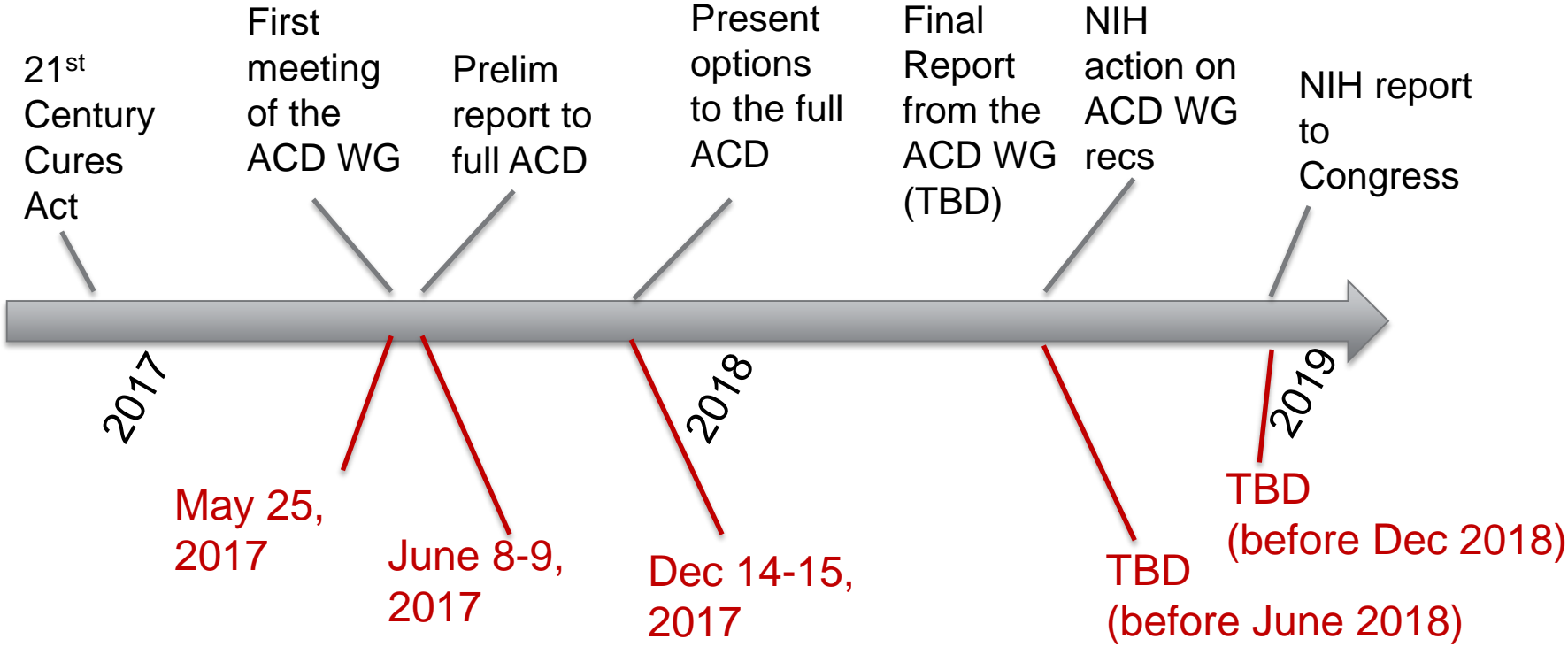
RPG Application and Review

Element of Rigor	Section of Application	Criterion Score	Additional Review Consideration	Contribute to Overall Impact?
Scientific Premise	Research Strategy	Significance	NA	Yes
Scientific Rigor		Approach	NA	Yes
Consideration of Relevant Biological Variables Such as Sex		Approach	NA	Yes
Authentication of Key Biological and/or Chemical Resources	New Attachment	NA	Adequate or Inadequate	No

January 2016



Timeline for ACD WG



- Application
 - Highlight what's important
 - Section(s) for rigor
 - Not just authentication
 - “CONSORT-like” checklist
 - Clarifies review priorities
- Resources
 - Validated, vetted materials

Trial design	3a
	3b
Participants	4a
	4b
Interventions	5
Outcomes	6a
	6b
Sample size	7a
	7b
Randomisation:	
Sequence	8a
generation	8b
Allocation	9
concealment	
mechanism	
Implementation	10
Blinding	11a

Options to Consider: Start with PHS 398

[View Burden Statement](#)

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 3/31/2020

Introduction				
1. Introduction to Application (for Resubmission and Revision applications)	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
Research Plan Section				
2. Specific Aims	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
3. *Research Strategy	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
4. Progress Report Publication List	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
Other Research Plan Section				
5. Vertebrate Animals	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
6. Select Agent Research	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
7. Multiple PD/PI Leadership Plan	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
8. Consortium/Contractual Arrangements	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
9. Letters of Support	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
10. Resource Sharing Plan(s)	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
11. Authentication of Key Biological and/or Chemical Resources	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
Appendix				
12. Appendix	<input type="text"/>	Add Attachments	Delete Attachments	View Attachments

Introduction

Research Plan

Other:
Vert animals
Select agent
MPI ...
Authentication

Appendix

Research Strategy = 12 pages



Option 1: New Attachment in Research Plan

Research Plan Section

2. Specific Aims

Add Attachment

Delete Attachment

View Attachment

3. *Research Strategy

Add Attachment

Delete Attachment

View Attachment

4. Progress Report Publication List

Add Attachment

Delete Attachment

View Attachment

Add section 5 here

Include **one document** with description of premise, rigor, and biological variables

Option 1 Considerations

Pros	Cons
<ul style="list-style-type: none">• Draws attention• Located in one place• With Research Plan• More space• Contribute to score*	<ul style="list-style-type: none">• Duplicate information entry• Free-form may miss key items• More content for review• OMB clearance

*Authentication Plan does not contribute to score



Option 2: New Headings in Research Strategy

Research Plan Section

2. Specific Aims

	Add Attachment	Delete Attachment	View Attachment
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3. *Research Strategy

	Add Attachment	Delete Attachment	View Attachment
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4. Progress Report Publication List

	Add Attachment	Delete Attachment	View Attachment
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Include headings with descriptions of premise, rigor, and biological variables

Option 2 Considerations

Pros	Cons
<ul style="list-style-type: none">• Draws attention• All in one location• With Research Plan• Neutral for review content• No need for OMB clearance• Contribute to score*	<ul style="list-style-type: none">• Duplicate information entry• Free-form may miss key items• Collision with page limits

*Authentication Plan does not contribute to score



[View Burden Statement](#) **PHS Rigor and Transparency Form**

Scientific Premise Describe the scientific premise for the proposed project.	<input type="text"/>	Fill-in or attachment
Scientific Rigor	<input type="text"/>	
Inclusion, Exclusion	<input type="text"/>	
Allocation	<input type="text"/>	
Blinding	<input type="text"/>	
Sample Size	<input type="text"/>	
Analysis Plans	<input type="text"/>	
Biological Variables Consideration of biological variables such as sex	<input type="text"/>	Fill-in or attachment

Include **detailed, separate documents** on premise, rigor, and biological variables
Collect granular information for scientific rigor

Option 3 Considerations

Pros	Cons
<ul style="list-style-type: none">• Draws attention• Specificity of items• Mix discrete and text• Easier to mine data• More space• Contribute to score*	<ul style="list-style-type: none">• Disconnect from Research Plan• Duplicate information entry• More content for review• Other rigor items?• OMB clearance

*Authentication Plan does not contribute to score



Antibody Validation Database

Home Targets Sources Validators Projects Upload About

enter the target name

search

Search examples: H3K9me3, H3K27me3, H3K4me3

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

Histone Modification Antibodies from Egelhofer et al, An assessment of histone-modification antibody quality, Nature Structural & Molecular Biology, 2010

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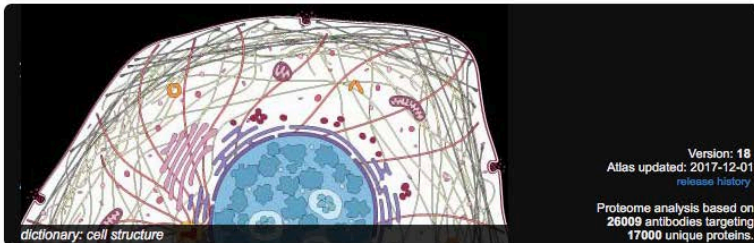
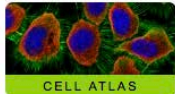
THE HUMAN PROTEIN ATLAS

MENU HELP NEWS

SEARCH

SEARCH [input] Search Fields >

e.g. RBM3, insulin, CD36



Version: 18
Atlas updated: 2017-12-01
[release history](#)

Proteome analysis based on
26009 antibodies targeting
17000 unique proteins.

Enhanced Antibody Validation

A new concept for enhanced validation of antibodies is launched. 10540 antibodies targeting 6787 proteins have been validated using at least one out of five validation strategies. The results of the enhanced validations are presented at the Antibody Info page of respective protein. [Read more](#)



Explore the Pathology Atlas

The Pathology Atlas allows the exploration of the consequence of genome-wide transcript levels for the clinical survival of patients across all major cancer types. Individual genes can be investigated using an interactive and open access database. The atlas is described in more detail by Uhlen et al "A pathology atlas of the human cancer transcriptome" in Science (August 18, 2017). [Read more](#)



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.

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TRAINING & CERTIFICATION

EVENTS

ABOUT US ▾

What is the reproducibility crisis?

There is a recent outpouring of concern among the scientific community. Recent findings suggest that ~ 50% of scientific literature is not reproducible, spending of ~28 billion dollars annually in the US alone¹.

Apart from wasted time and money, invalidated research diminishes trust. These alarming facts provoked serious introspection and discussion among universities and industry partners to identify the core causative factors and best practices to avert the situation.

Novel Antibody Scoring System Enters Alpha Testing



<https://www.benchsci.com/reproducibility/>

<https://www.gbsi.org/news/novel-antibody-scoring-system-enters-alpha-tests/>



Novel Antibody Scoring System Enters Alpha Testing
Evaluating and Ranking Performance Will Help Scientists Tailor Antibody Selection to Specific Research Experiments

A Kind of Consumer Reports?

bioz



Added Terms: cell, cell lines, cells, lines cell...

Home > Search Results > cell line

Products

Sponsored ⓘ

Anti-PD-L1 (Bio X Cell)



 **99 / 100** **Bio Stars**  **Techniques**

Epigenetic silencing of Th1 type chemoki... (Nature 2016 Apr 30)
".. or 10 mg/kg **anti-PD-L1 (B7-H1, clone 10F.9G2, BE0101, Bio X Cell)** three times per .." (More...)

[Protocol Conditions](#) | [Articles](#)

Sponsored ⓘ



MitoSOX™ Red Mitochondrial Superoxide Indicator, for live-cell imaging (Thermo Fisher Scientific / Life Technologies)

 **99 / 100** **Bio Stars**  **Techniques**

The amino acid sensor GCN2 controls gut ... (Nature 2016 Aug 31)
".. preparation was incubated with **mitosox (M36008, Life technologies)** for 15 minutes (manufacturers instructions)." (More...)

[Protocol Conditions](#) | [Articles](#)



TUBO cell line FCS (PAN - Biotech)

 **96 / 100** **Bio Stars**  **Techniques**

Early dissemination seeds metastasis in ... (Nature 2017 May 31)
".. (Pan-Biotech: P04-03500) supplemented with 10% (20% for **TUBO cell line) FCS (Pan-Biotech: P30-3702)**, 2 mmol/L L-glutamine (Pan-Biotech: .." (More...)

[Protocol Conditions](#) | [Articles](#)



MIA PaCa-2 cells (ATCC)

 **99 / 100** **Bio Stars**  **Techniques**

The Necrosome Promotes Pancreas Oncogene... (Nature 2016 Sep 30)
".. lines AsPC1, PANC1, and **MIA PaCa-2 cells** (gifts of Dafna Bar-Sagi, originally obtained from **ATCC**) were maintained in complete .." (More...)

[Protocol Conditions](#) | [Articles](#)

Cell Recovery Solution (Corning)

 **99 / 100** **Bio Stars**  **Techniques**

Wnt/β-catenin promotes gastric fundus sp... (Nature 2017 Jun 30)
".. collected and incubated in **Cell Recovery Solution (Corning)** for one hour at 4°C then washed in PBS. ..." (More...)

[Protocol Conditions](#) | [Articles](#)

VENDORS (40)

- Cell Signaling
- Thermo Fisher
- Bio X Cell
- ATCC
- MilliporeSigma
- BD Biosciences
- Fluidigm
- STEMCELL Technologies
- + Show More

TECHNIQUES (33)

- Incubation
- Stain
- Cell Culture
- WB
- + Show More

ARTICLES



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

<https://grants.nih.gov/grants/guide/pa-files/PAR-17-341.html>



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

<https://grants.nih.gov/grants/guide/pa-files/PAR-17-341.html>



- 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 ...

<https://grants.nih.gov/grants/guide/pa-files/PAR-17-341.html>



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

<https://grants.nih.gov/grants/guide/pa-files/PAR-17-341.html>



- 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?