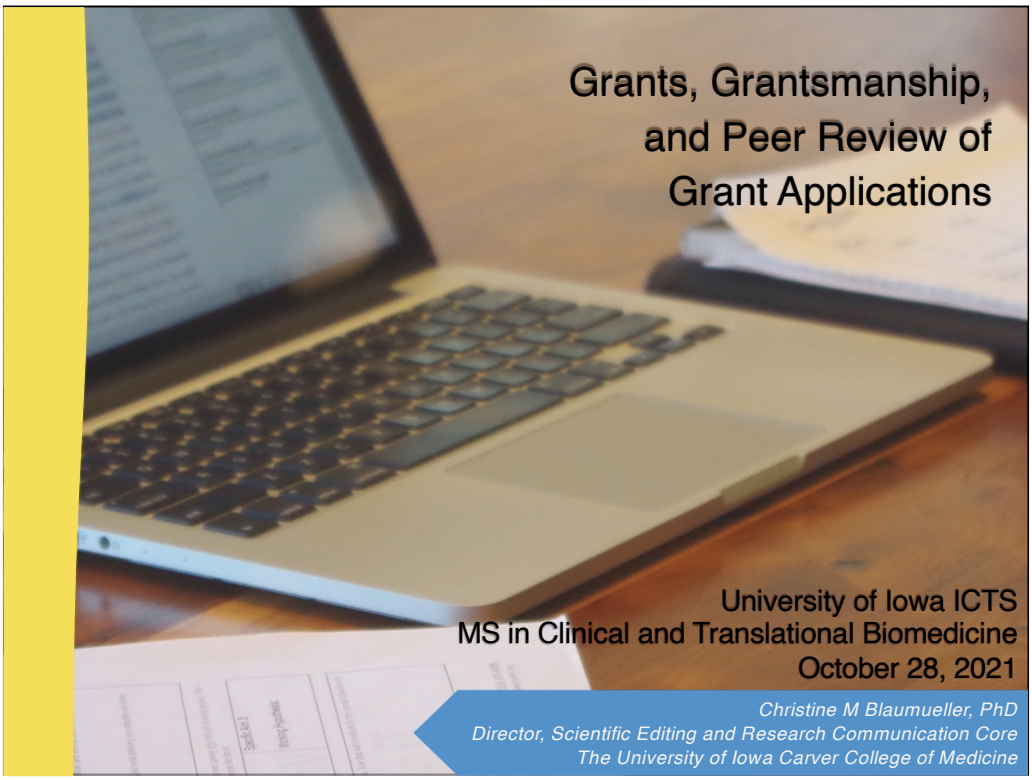
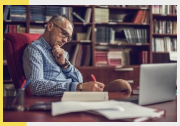

Grants, Grantsmanship, and Peer Review of Grant Applications
University of Iowa ICTS
MS in Clinical and Translational Biomedicine
October 28, 2021
Christine M Blaumueller, PhD
Director, Scientific Editing and Research Communication Core
The University of Iowa Carver College of Medicine

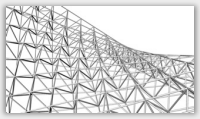
Topics



Grants:
Mechanisms and Review at NIH

Grantsmanship:
Structuring the Specific Aims Page

Considerations for the Innovation Section



Grantsmanship and Rigor/Reproducibility:

The Significance Section

The Approach Section

Resources

Here's what I plan to cover

- Doing sort of a survey of the relevant information so that you can find the appropriate resources when the time comes
- So if you want to dig deeper into any point – Feel free to ask questions as we go.

Expectations of NIH Research (R) and Career (K) grants

- R Grants

  Have a sustained, powerful influence on the research field(s) involved

- K Grants:

  Enhance candidate's potential for a productive, independent scientific career in a health-related field

The first thing you should know about a funding mechanism is its purpose…

Examples of Research (R) Grant Types

R01: Research Project Grants

- mature awards
- 4–5 years of independent support
- 12-page Research Strategy

R21: Exploratory/Developmental Grants

- High-risk grants
- 2 years
- 6-page Research Strategy

R03: Small Grant Projects

- Pilot/Feasibility studies, Secondary analysis
- 2 years
- "small" grant, tightly focused, self-contained
- small budget
- 6-page Research Strategy

For more on review criteria and scoring system, see: http://grants.nih.gov/grants/peer-review.htm

A few examples of what add up to quite a few mechanisms

- All have different goals, durations, requirements in writing
- Make sure you're clear on this – have seen lots of negative reviews of R21s because reviewers felt the fit was poor

___

R01 is best known – usually in ***support of a research program for a whole lab***

- R01 (unlimited, up to 250K/yr), up to 5 years

R21 also common – harder to get

- (up to 275K, up to 200K/yr), up to 2 years
- Fewer are given out and LOTS of people apply
- Expectations are very high!

R03 (100K):

- Pilot or feasibility studies
- Secondary analysis of existing data
- Small, self-contained research projects
- Development of research methodology or new research technology

Examples of Career (K) Grant Types:

K01: Mentored Research Scientist Career Development

- For postdocs or early-career research scientists
  - committed to research
  - needing advanced research training and additional experience
- 12-page Career Goals plus Research Strategy

K08: Mentored Clinical Scientist Research Career Development

- Fill academic faculty gap in health sciences by supporting
  - clinician scientists, promising as independent investigators
  - faculty members
- 12-page Career Goals plus Research Strategy

K99: Pathway to Independence

- For postdocs seeking independent research positions
- Supports:
  - initial mentored research experience (K99)
  - subsequent independent research (R00)
- Must compete for independent R01 support (R00 phase)

- Even more subtypes than Rs
- Lots of variety regarding goals
  - For clinicians to learn science
  - For scientists needing additional experience
  - A springboard for junior scientists from K to R grants
  - again, CHOOSE ONE THAT's A GOOD FIT
- Generally shorter than R01 as far as research component

How Research (R) and Career (K) grants are evaluated

- Overall impact score assesses:
  - R grants: *likelihood that project will have a sustained, powerful influence on the research field(s) involved*
  - K grants: *likelihood that the proposed career development will enhance candidate's potential for a productive, independent scientific career in a health-related field*
- Core review criteria for impact score by application type:

K Grants
- Candidate
- Career Development Plan/Goals
- Research Plan
- Research Plan Mentors
- Environment and Institutional Commitment

R Grants
- Significance
- Investigator(s)
- Innovation
- Approach
- Environment

https://www.nichd.nih.gov/grants-contracts/training-careers/extramural/career

Grant review – Effectiveness is evaluated as "Overall Impact Score"

- How well the proposal supports the likelihood that…
- This score is derived from an evaluation of 5 criteria
- Criteria differ across grant types
- For Rs, likelihood that project will have a sustained and powerful influence is evaluated based on
  - (science is evaluated mainly on Significance and Approach in Research Plan)
- For Ks, likelihood that training will enhance candidate's potential
  - (science is evaluated mainly in Research Plan)

Scored Review Criteria by Grant Type

Fellowship (F)

- Applicant
- Sponsors, Collaborators, Consultants
- Research Training Plan
  - Proposed Research
  - Training plan
- Training Potential
- Environment & Inst. Commitment to Training

Career (K)

- Career Development Plan/Career Goals
- Research Plan
- Mentor(s), Co-Mentor(s)…
- Environment Commitment to the Candidate

Research (R)

- Significance
- Investigator
- Innovation
- Approach
- Environment

Evaluation of the Science

For more on review criteria and scoring system, see: http://grants.nih.gov/grants/peer-review.htm

Here is a comparison of the 5 scored review criteria for F, K and R and have highlighted:

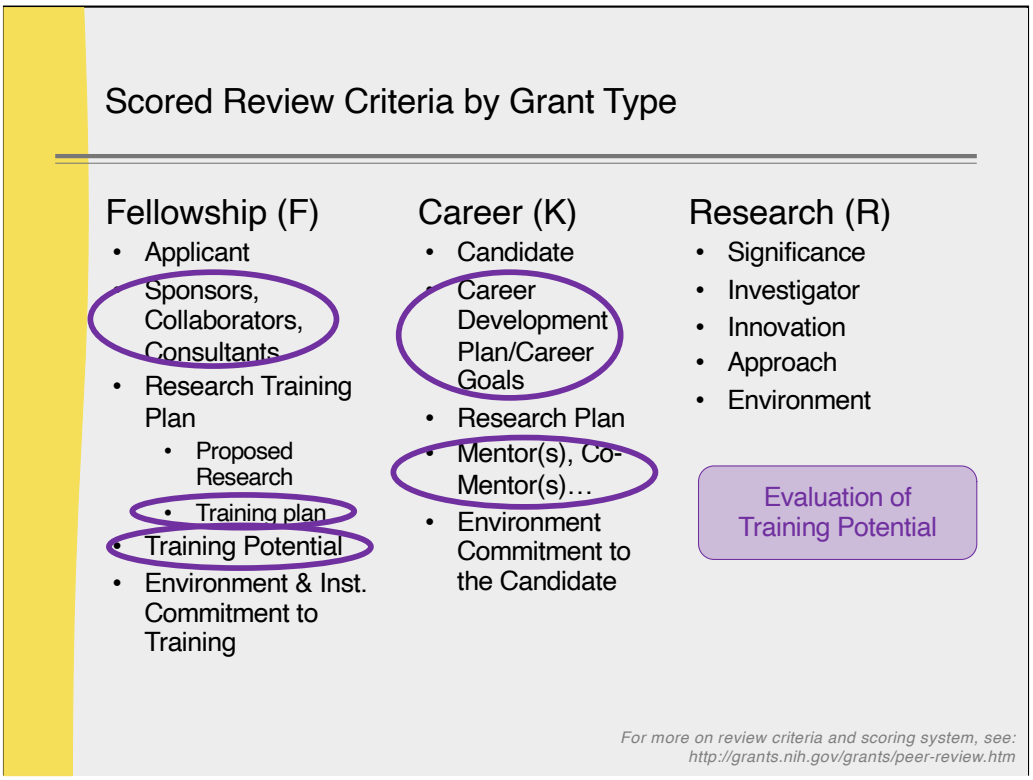
- ***where the science is evaluated*** (as I've touched on already)
- Note differences from R grant to F grants –
  - R => Significance/Innovation/Approach all get own scores in evaluating the science.
  - K => Research Plan is evaluated as a unit (no separate scores for Significance/Innovation/Approach in evaluating the science)
  - F => Proposed Research is only half of one of the 5 criteria (no separate scores for Significance/Approach and shared with Training Plan)

Questions about the Science:

- Are proposed research questions/design/methodology of significant scientific and technical merit?
- Is key support for project (prior research) rigorous?
- Plans to address weaknesses in rigor of prior research?
- Strategies to ensure robust and unbiased approach?
- Plans to address relevant biological variables?
- Is plan relevant to candidate's research career objectives?
- Is plan appropriate to stage of development and vehicle for developing research skills described in career development plan?
- Will any proposed clinical trial experience contribute to proposed research project?

Mentored Clinical Scientist Research Career Development Award
(Parent K08 Independent Clinical Trial Not Allowed)
PA-19-117, Jan 2019-Jan 2022

Questions asked about the science are the following or this plus a few additional questions, depending on the mechanism



Here I've highlighted:

- ***where the training that's proposed is evaluated***

- BIG difference between these and R grants!
  - Not relevant in Rs
  - Two sections contribute in Ks
  - Three sections contribute in Fs

Questions about Proposed Training:

- Likelihood that plan will contribute substantially to scientific development and lead to scientific independence?
- Are prior training and research experience appropriate for this award?
- Are content, scope, phasing, and duration appropriate relative to:
  - prior training/research experience and stated training
  - and research objectives for achieving research independence?
- Are plans for monitoring and evaluating the candidate's research and career development progress adequate?
- Will any proposed clinical trial experience contribute to applicant's research career development?

Mentored Clinical Scientist Research Career Development Award
(Parent K08 Independent Clinical Trial Not Allowed)
PA-19-117, Jan 2019-Jan 2022

These questions are about both:

Proposed training...

Questions about Proposed Trainers:

- Is mentor qualified in the proposed area of research?
- Does mentor adequately address candidate's potential, strengths, and areas improvement?
- Is description of quality and extent of mentor's role adequate?
- Is mentor's description of activities, including formal course work, adequate?
- Evidence of experience fostering development of independent investigators?
- Evidence of current research productivity/peer-reviewed support?
- Adequate support for proposed research project (active/pending)?
- Adequate plans for monitoring/evaluating progress to independence?
- Is any clinical trial supported by mentor expertise/experience/ability?

Mentored Clinical Scientist Research Career Development Award
(Parent K08 Independent Clinical Trial Not Allowed)
PA-19-117, Jan 2019-Jan 2022

...and proposed trainer

Scored Review Criteria by Grant Type

Fellowship (F)

- Applicant
- Sponsors, Collaborators, Consultants
- Research Training Plan
  - Proposed Research
  - Training plan
- Training Potential
- Environment & Inst. Commitment to Training

Career (K)

- Candidate
- Career Development Plan/Career Goals
- Research Plan
- Mentor(s), Co-Mentor(s)…
- Environment Commitment to the Candidate

Research (R)

- Significance
- Investigator
- Innovation
- Approach
- Environment

Evaluation of the Applicant

For more on review criteria and scoring system, see: http://grants.nih.gov/grants/peer-review.htm

The applicant is evaluated in all three types of grants

Questions about Applicant/Candidate:

- Are they likely to become an independent and productive researcher?
- Are their prior training and research experience appropriate?
- Are their academic, clinical (if relevant), and research records of high quality?
- Is there evidence of their commitment to becoming independent research investigator?
- Do letters of reference provide evidence of high potential for candidate to become an independent investigator?

Mentored Clinical Scientist Research Career Development Award
(Parent K08 Independent Clinical Trial Not Allowed)
PA-19-117, Jan 2019-Jan 2022

My synopsis of the questions reviewers are asked

- i.e. what authors need to be sure to address explicitly

Scored Review Criteria by Grant Type

Fellowship (F)

- Applicant
- Sponsors, Collaborators, Consultants
- Research Training Plan
  - Proposed Research
  - Training plan
- Training Potential
- Environment & Inst. Commitment to Training

Career (K)

- Candidate
- Career Development Plan/Career Goals
- Research Plan
- Mentor(s), Co-Mentor(s)…
- Environment Commitment to the Candidate

Research (R)

- Significance
- Investigator
- Innovation
- Approach
- Environment

Evaluation of Environment and Inst Commitment

For more on review criteria and scoring system, see: http://grants.nih.gov/grants/peer-review.htm

Finally, in all cases, the NIH wants to know if the applicant has sufficient support for the proposed project.

Questions about Environment/Institutional Commitment:

- Is commitment to reasonable %effort (direct) to described research adequate? Is remaining %effort balanced between research, teaching, administrative, and clinical responsibilities?
- Strong institutional commitment to career development?
- Adequate research facilities, resources, and training opportunities, including faculty capable of productive collaboration with candidate?
- High quality environment for scientific and professional development?
- Assurance that candidate will be integral part of institution's research program as independent investigator?

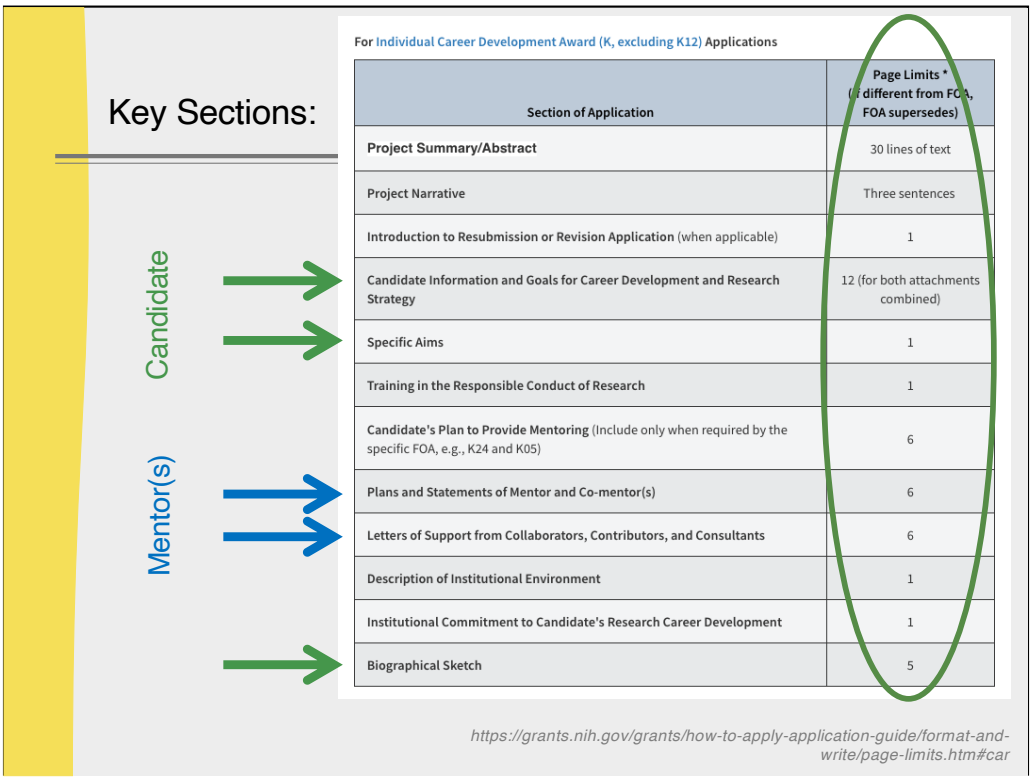
Mentored Clinical Scientist Research Career Development Award
(Parent K08 Independent Clinical Trial Not Allowed)
PA-19-117, Jan 2019-Jan 2022

Environment & Institutional Commitment to the Candidate:

Just want to highlight that for K grants,

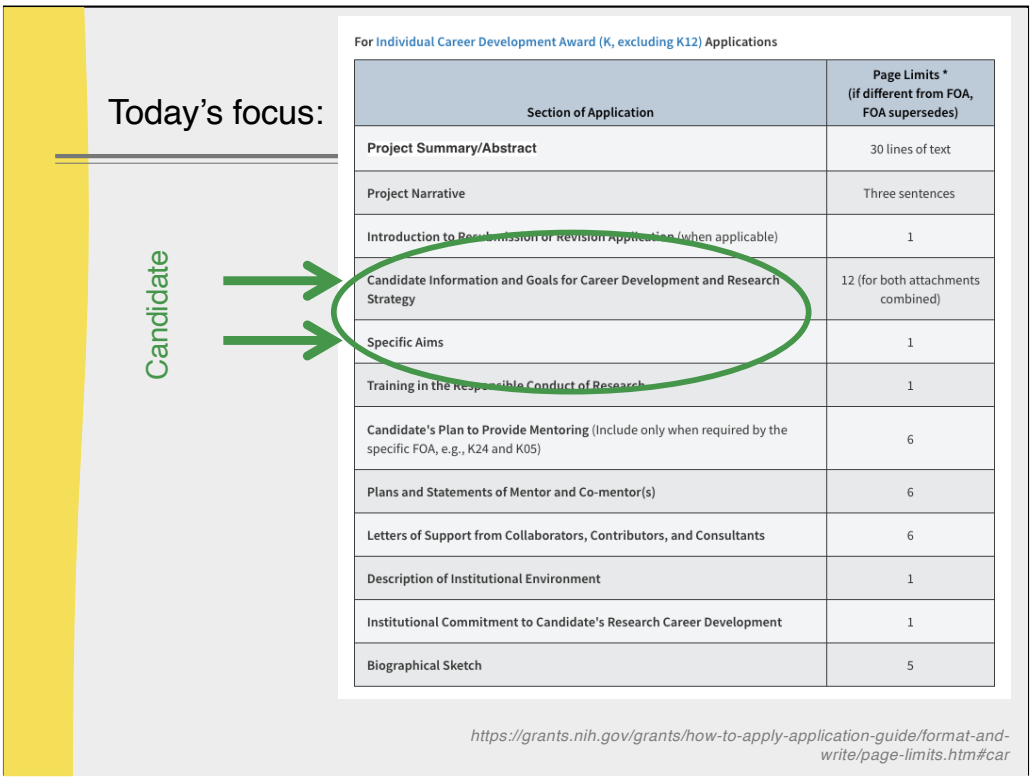
It's important to show that your department will give you sufficient protected time to do the research

especially if you are a clinician



For those of you writing K grants:

- These are some of the key sections you and your mentors will need to prepare
- Don't ignore the ones without arrows
- and here are the page limits



For Individual Career Development Award (K, excluding K12) Applications

Section of Application	Page Limits * (if different from FOA, FOA supersedes)
Project Summary/Abstract	30 lines of text
Project Narrative	Three sentences
Introduction to Resubmission or Revision Application (when applicable)	1
Candidate Information and Goals for Career Development and Research Strategy	12 (for both attachments combined)
Specific Aims	1
Training in the Responsible Conduct of Research	1
Candidate's Plan to Provide Mentoring (Include only when required by the specific FOA, e.g., K24 and K05)	6
Plans and Statements of Mentor and Co-mentor(s)	6
Letters of Support from Collaborators, Contributors, and Consultants	6
Description of Institutional Environment	1
Institutional Commitment to Candidate's Research Career Development	1
Biographical Sketch	5

https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/page-limits.htm#car

Here are the ones I'll focus on through the rest of the talk

- Note that where R grants have a 12-page Research Strategy
- K grants have the Research Strategy combined with Candidate Info/Goals – in the same amount of space

Scientific sections of K and R grants *

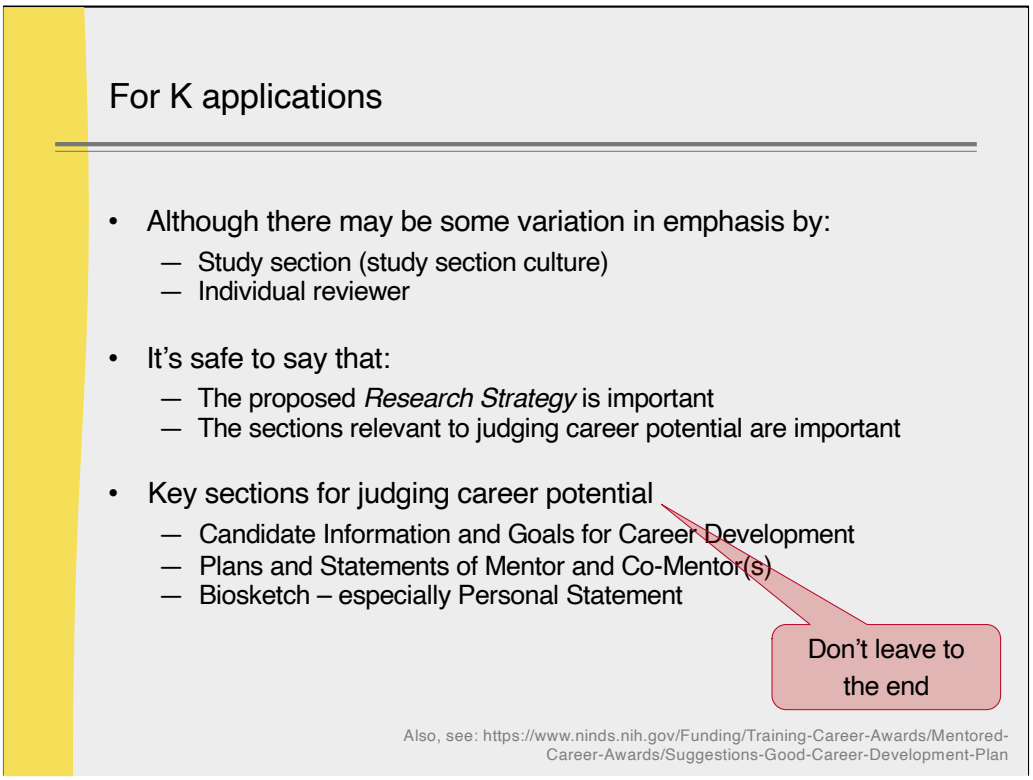
K Grants	R Grants
• Specific Aims page	• Specific Aims page
• Candidate Information and Goals for Career Development and Research Strategy:	• Research Strategy:
— Candidate's Background — Candidate's Career Goals and Objectives — Candidate's Plan for Career Development/ Training Activities during Award Period — Significance — [Innovation] — Approach	— Significance — Innovation — Approach

Recommend 6 + 6

Also, see: https://www.ninds.nih.gov/Funding/Training-Career-Awards/Mentored-Career-Awards/Suggestions-Good-Career-Development-Plan

This is a breakdown:

- Although there is no formal recommendation for how to split this in a K,
- we recommend starting with the idea of 6+6



Here are some insights we've gained during previous discussions with panelists who have served on study sections evaluating training grants (F30/F31).

- Also relevant to K grants

What happens during review at NIH?

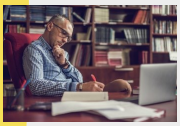
- 2–3 reviewers among ~ 20 panel members will read in entirety
- these reviewers will present and discuss it at meeting and give it a preliminary impact score
- they may revise opinions based on discussion
- non-presenting reviewers will get main overview from Specific Aims page
- all reviewers contribute to final overall impact score

➥ Ultimately, even reviewers who read little more than your Specific Aims page have a major influence on your score!

Start out by talking about what happens in study sections…

- As you may know, NIH study sections are large
- go for a couple of days
- Disrupt the reviewers' schedule (preparation and meeting time
- What a non-presenting reviewer relies on is:
    - Discussion
    - Aims page (or Abstract) – use as "roadmap" during discussion

Topics



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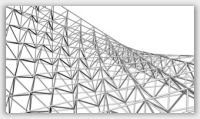


Grantsmanship and Rigor/Reproducibility:

The Significance Section

The Approach Section

Resources

Writing an effective Specific Aims page requires

time and practice...

The present letter is a very long one, simply because I had no leisure to make it shorter.

Blaise Pascal (1623-1662)

French scientist, mathematician, Physicist, philosopher, moralist & writer

Something to remember about the Specific Aims page

- It's hard to write because you're expected to fit a lot of information into a single page (think of this as a roadmap)
- It would be a lot easier if you had a few pages – but that would defeat the purpose
- Remember **– *tell a story***!

Specific Aims section examples

1. Which proposal was most inviting?
2. Which proposal was most informative?
3. What strategies (in any example) were effective?
4. What aspects (of any example) need improvement?

Just want to very briefly get your thoughts about the three examples you were asked to read before class...

- Which was most inviting?
- Which was most informative?
- What approaches to the writing you did find helpful?
- What approaches did you not find helpful?

Example 1

NIH: Smalls-Mantey, Sample F31 Application and Summary Statement (formatting altered from original)
https://www.niaid.nih.gov/grants-contracts/smalls-mantey-sample-f31-application-summary-statement#aims

Specific Aims

Understanding the basis of an immune response that controls infection or provides sterilizing immunity remains a major goal in the search for effective vaccines or immunotherapies for HIV. Antibodies (Abs) induced by candidate vaccines to the surface envelope glycoprotein have not neutralized a broad array of primary virus isolates. For this reason, eliciting a cytotoxic cellular response has been the primary goal in most recent vaccine trials. However, this approach has not been successful in containing viral replication in vaccinees that have become HIV-infected. Antibody-dependant cellular cytotoxicity (ADCC) has been shown to mediate sterilizing immunity against challenge with pathogenic simian immunodeficiency virus [Hessel 2007]. In ADCC, Fc-bearing Abs bind viral epitopes coating an infected CD4+ target T cell and an Fc receptor bearing effector, most commonly natural killer cells (NKs), bind the Ab and use perforin to deliver granzymes which induce apoptosis in the target. We want to study ADCC in infected patients to understand the magnitude and characteristics of the best responses achieved by natural infection. First, we will compare ADCC mediated by the sera of a cohort of patients using a granzyme B cytotoxicity assay developed in our lab. Based on these findings, we will select the sera of patients with the most ADCC, generate monoclonal Abs (mAbs), and characterize the mAbs based on epitope specificity, affinity, potency, breadth, IgG isotype, and Fc type. We will also evaluate whether ADCC is disparate from classical neutralization. Finally we will use microscopy to examine the synapse between effectors, Abs, and targets. The outcome of this research will provide insight into the characteristics of Abs that mediate ADCC that are likely important goals in the design of HIV vaccines or immunotherapies.

Hypothesis: Antibody-dependent cellular cytotoxicity (ADCC) is a function that has been shown to mediate protection from lentiviral infection. We hypothesize that variation in ADCC activity of sera are dictated by the amount, specificity, and subclass of HIV-specific antibodies.

Aim 1: Characterize the potency of sera of HIV-infected individuals in ADCC.

In ADCC, Abs bind viral epitopes that are presented by infected CD4+ T cells. NKs expressing an Fc receptor bind the Fc domain of the Ab and use perforin to deliver granzymes to the HIV-infected cell. Subsequently, granzymes induce apoptosis within the cell. Our lab has developed a flow cytometric assay that measures granzyme B delivered to an HIV-infected CD4+ target T cell. We will classify ADCC by the percent of target cells receiving granzyme and the elimination of targets as defined by residual percent of targets expressing p24, HIV capsid.

1. Compare the serum of HIV+ individuals with various rates of progression and viral loads to determine which contain Abs capable of mediating the highest levels of ADCC.
2. Compare the ADCC and neutralizing activity of patient sera.

Aim 2: Characterize the specificity and breadth of antibodies with ADCC activity. Our laboratory has panels of NAbs derived from patients with known serum neutralizing or ADCC-mediating activity.

1. Determine whether recognition of specific epitopes is required for ADCC.
2. Define the breadth of the polyclonal sera by its ability to mediate ADCC in CD4+ T cells infected by different clades of HIV.
3. Titer serum total IgG, IgG1, and IgG3 binding infected CD4+ T cells.

Aim 3: Characterize the structure and function of the target-effector synapse.

Using both fixed and live cell laser scanning confocal microscopy (LSCM), transmission electron microscopy (TEM) and cryo-electron microscopy (cryo-EM) and tomography, we will examine the synapse formed between NK and other cells with potential ADCC activity (macrophages and neutrophils) and infected target cells. We will specifically investigate:

1. The structure of a functional ADCC synapse.
2. The kinetics of ADCC function in real time and its relation to antibody type and specificity.
3. A role for antibody-dependent cell-mediated phagocytosis (ADCP) in elimination of HIV-infected cells.
4. Receptors and effector molecules central to ADCC activity against HIV infected cells.

PI: Smalls-Mantey, Adjoa R. Grantee Org: Columbia University Health Sciences; Funded by NIH NIAID
The text of this application is copyrighted. You may use it only for nonprofit educational purposes.

Effective

1. Problem sounds interesting to NIH
2. Great first sentence – and focus is on biology without needing to invoke the number of affected patients.

Could be improved

1. Logic breaks down in paragraph 1.
2. Lots of detail at the expense of the big picture
3. Some information is redundant
4. Aims sound more descriptive than they probably are
5. Unclear what the expected outcomes will be and how this particular information will move the field forward.

Example 2

NIH: Calix, Sample F31 Application and Summary Statement (formatting altered from original)
https://www.niaid.nih.gov/grants-contracts/calix-sample-f31-application-and-summary-statement

Specific Aims

Rationale: Serotype 11E is a novel pneumococcal serotype, previously unidentified due to its serological similarity to the epidemiologically prevalent 11A, a significant serotype in both asymptomatic carriage and disease-causing strains. Genetic findings indicate that each 11E strain emerged independently in separate hosts. 11E differs from 11A due to a disruption of the wcjE capsule synthesis gene, which encodes an Oacetyltranferase that targets 1-phosphoglycerol in capsule polysaccharide. We hypothesize that disruption of the gene allows a strain initially expressing 11A capsule to avoid a host humoral response by changing its capsule structure, resulting in an 11E infection. Given that no previous studies have recognized 11E as a separate serotype, we aim to determine the extent of the role 11E plays following initial 11A infection, setting the stage for future studies addressing the prevention and control of disease caused by serotype 11A.

Aim 1. Examine nasopharyngeal (NP) isolates for the presence of 11E strains
(1A) Develop a FACS-based assay for efficient detection and distinction of 11A and 11E strains.
(1B) Identify additional 11E clinical strains, focusing on NP isolates originally typed as serotype 11A.
(1C) Examine newly identified 11E isolates for heterogeneity of wcjE disruption.

Aim 2. Determine whether a human humoral immune response can be selective for 11A and not 11E in vitro
(2A) Generate isogenic 11A and 11E strains for comparative studies.
(2B) Determine antibody specificity for 11A or 11E PS in sera from individuals vaccinated with the pneumococcal vaccine PPV-23 (PPV-23 sera) by using ELISA.
(2C) Detect functional anti-11A and anti-11E antibodies in PPV-23 sera by using Single Opsonophagocytic Killing Assay (SOPKA) of 11A and 11E.
(2D) Determine competitive advantage of 11E by immunological escape in PPV-23 sera by using Multiplex Opsonophagocytic Killing Assay (MOPKA).
(2E) Verify the role of anti-capsular PS antibodies in 11A and 11E opsonization.

Aim 3. Determine that 11E has a selective advantage in an immune response against 11A in vivo and whether 11E infection emerges from initial infection with 11A
(3A) Develop an 11A and 11E mouse infection model.
(3B) Detect total and functional anti-11A and anti-11E antibodies in murine sera following 11A and 11E infection.
(3C) Determine in vivo survival of 11A and 11E in mice actively immunized against 11A and 11E PS.
(3D) Assess in vivo survival of 11A and 11E in mice passively immunized with 11A-specific monoclonal antibodies.

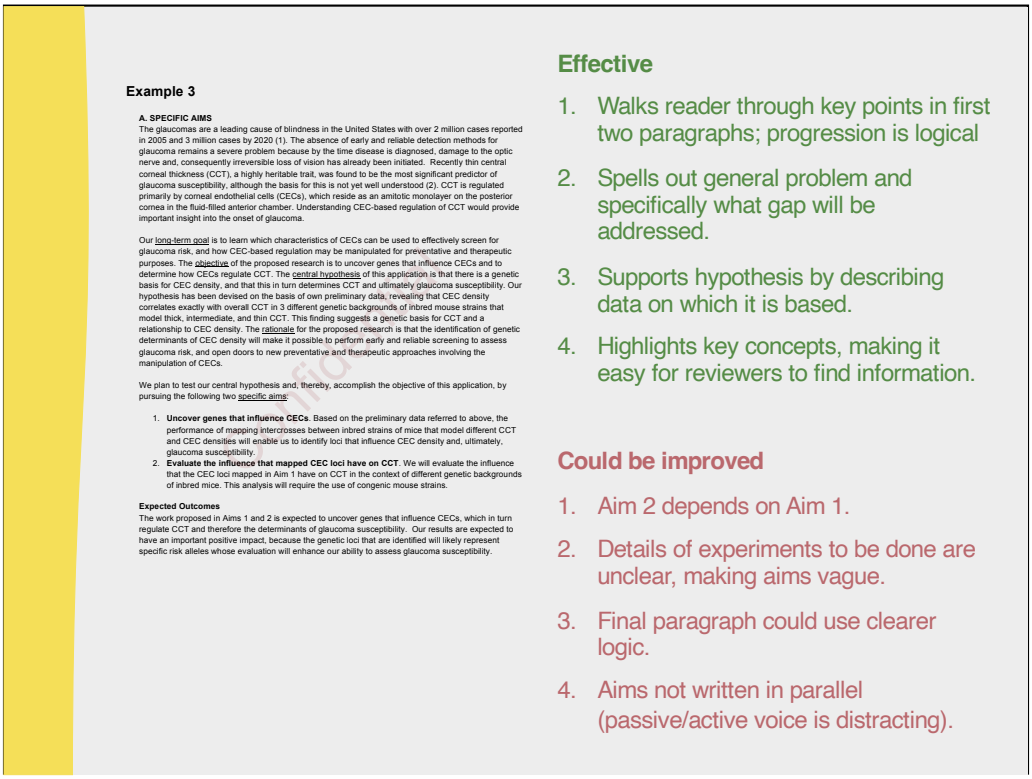
PI: Calix, Juan; Grantee Org: University of Alabama at Birmingham; Funded by NIH NIAID
The text of this application is copyrighted. You may use it only for nonprofit educational purposes.

Effective

1. Topic likely of interest to NIH
2. Studies are both *in vivo* and *in vitro*.

Could be improved

1. Unclear exactly what the key gap in knowledge is and how the study will move the field forward.
2. Aims are list-like and lack of linkage and detail makes it hard to understand how they fit together.
3. ”Examine”, “Determine whether”, “Determine that” in aims titles are problematic.
4. Unclear what the expected outcomes will be.



Example 3

A. SPECIFIC AIMS

The glaucomas are a leading cause of blindness in the United States with over 2 million cases reported in 2005 and 3 million cases by 2020 (1). The absence of early and reliable detection methods for glaucoma remains a severe problem because by the time disease is diagnosed, damage to the optic nerve and, consequently irreversible loss of vision has already been initiated. Recently thin central corneal thickness (CCT), a highly heritable trait, was found to be the most significant predictor of glaucoma susceptibility, although the basis for this is not yet well understood (2). CCT is regulated primarily by corneal endothelial cells (CECs), which reside as an amitotic monolayer on the posterior cornea in the fluid-filled anterior chamber. Understanding CEC-based regulation of CCT would provide important insight into the onset of glaucoma.

Our long-term goal is to learn which characteristics of CECs can be used to effectively screen for glaucoma risk, and how CEC-based regulation may be manipulated for preventative and therapeutic purposes. The objective of the proposed research is to uncover genes that influence CECs and to determine how CECs regulate CCT. The central hypothesis of this application is that there is a genetic basis for CEC density, and that this in turn determines CCT and ultimately glaucoma susceptibility. Our hypothesis has been devised on the basis of own preliminary data, revealing that CEC density correlates exactly with overall CCT in 3 different genetic backgrounds of inbred mouse strains that model thick, intermediate, and thin CCT. This finding suggests a genetic basis for CCT and a relationship to CEC density. The rationale for the proposed research is that the identification of genetic determinants of CEC density will make it possible to perform early and reliable screening to assess glaucoma risk, and open doors to new preventative and therapeutic approaches involving the manipulation of CECs.

We plan to test our central hypothesis and, thereby, accomplish the objective of this application, by pursuing the following two specific aims:

1. **Uncover genes that influence CECs**. Based on the preliminary data referred to above, the performance of mapping intercrosses between inbred strains of mice that model different CCT and CEC densities will enable us to identify loci that influence CEC density and, ultimately, glaucoma susceptibility.
2. **Evaluate the influence that mapped CEC loci have on CCT**. We will evaluate the influence that the CEC loci mapped in Aim 1 have on CCT in the context of different genetic backgrounds of inbred mice. This analysis will require the use of congenic mouse strains.

Expected Outcomes

The work proposed in Aims 1 and 2 is expected to uncover genes that influence CECs, which in turn regulate CCT and therefore the determinants of glaucoma susceptibility. Our results are expected to have an important positive impact, because the genetic loci that are identified will likely represent specific risk alleles whose evaluation will enhance our ability to assess glaucoma susceptibility.

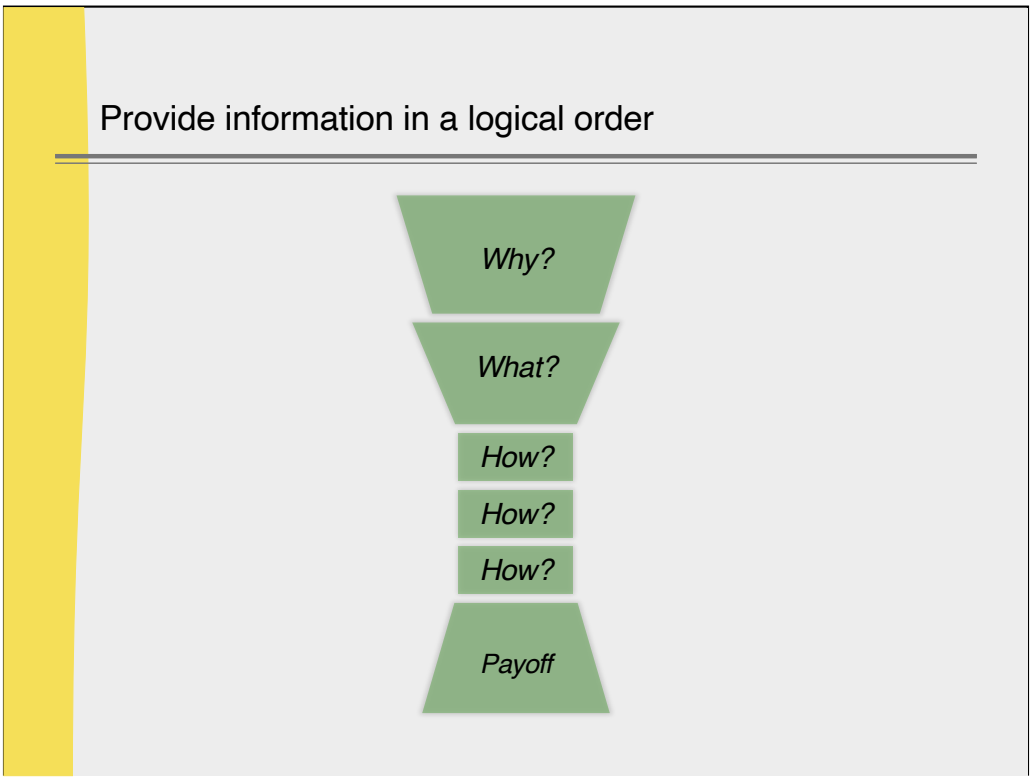
Effective

1. Walks reader through key points in first two paragraphs; progression is logical
2. Spells out general problem and specifically what gap will be addressed.
3. Supports hypothesis by describing data on which it is based.
4. Highlights key concepts, making it easy for reviewers to find information.

Could be improved

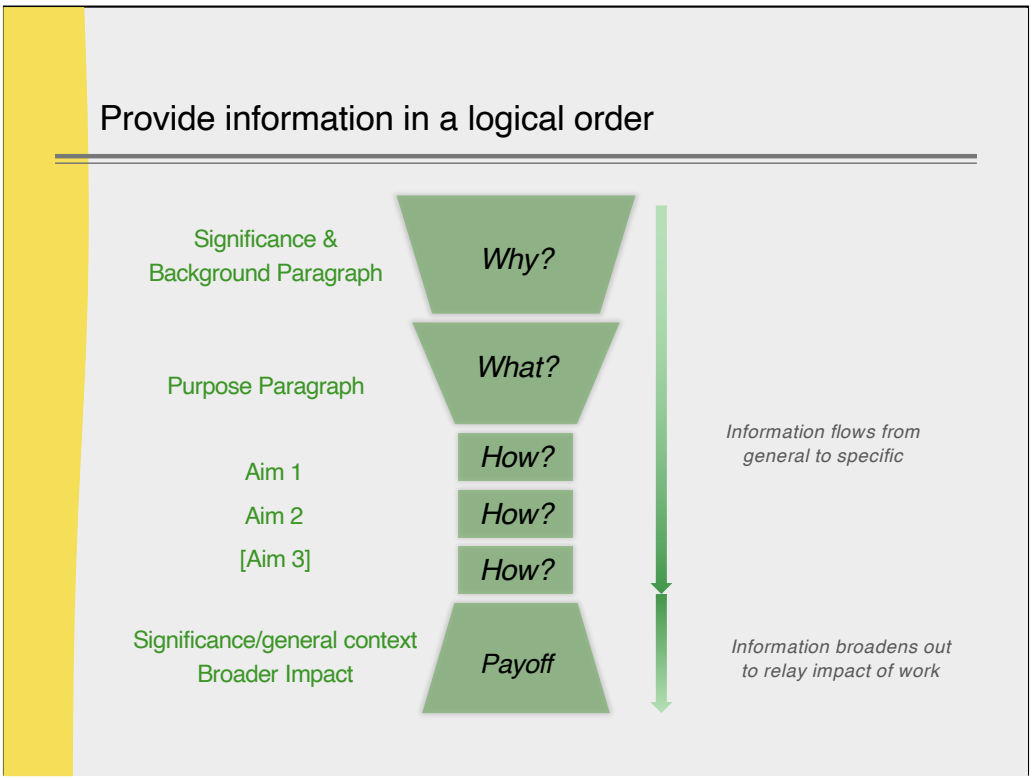
1. Aim 2 depends on Aim 1.
2. Details of experiments to be done are unclear, making aims vague.
3. Final paragraph could use clearer logic.
4. Aims not written in parallel (passive/active voice is distracting).

This one is the best attempt to tell a story



Now I'll go through a summary based on grant-writing workbook (reference is at the end of this talk)

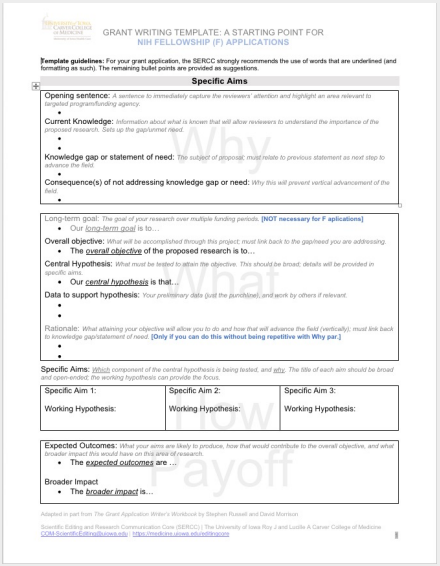
- Order of presentation designed to get the reader interested in the big-picture/problem before inundating them with details
- Writers often forget the need for this in their own work – but not typically when they read that of others!
- Continues with What they are setting out to do
- How they plan to do it
- And how the funding agency will be rewarded for its investment



- Keep in mind:
  - The purpose of each paragraph
  - Key elements and how the order pulls a logical thread through

Generate an Outline

- Helps make the logic of project clear to the reader
- Helps link ideas effectively and avoid excess detail



GRANT WRITING TEMPLATE: A STARTING POINT FOR
NIH FELLOWSHIP (F) APPLICATIONS

Template guidelines: For your grant application, the SERCC strongly recommends the use of words that are underlined (and formatting as such). The remaining bullet points are provided as suggestions.

Specific Aims

Opening sentence: *A sentence to immediately capture the reviewers' attention and highlight an area relevant to targeted program/funding agency.*

Current Knowledge: *Information about what is known that will allow reviewers to understand the importance of the proposed research. Sets up the gap/unmet need.*

Knowledge gap or statement of need: *The subject of proposal; must relate to previous statement as next step to advance the field.*

Consequence(s) of not addressing knowledge gap or need: *Why this will prevent vertical advancement of the field.*

Why

Long-term goal: *The goal of your research over multiple funding periods.* **[NOT necessary for F aplications]**

- *Our long-term goal* is to…

Overall objective: *What will be accomplished through this project; must link back to the gap/need you are addressing.*

- The *overall objective* of the proposed research is to…

Central Hypothesis: *What must be tested to attain the objective. This should be broad; details will be provided in specific aims.*

- Our *central hypothesis* is that…

Data to support hypothesis: *Your preliminary data (just the punchlines), and work by others if relevant.*

Rationale: *What attaining your objective will allow you to do and how that will advance the field (vertically); must link back to knowledge gap/statement of need.* **[Only if you can do this without being repetitive with Why par.]**

What

Specific Aims: *Which component of the central hypothesis is being tested, and why. The title of each aim should be broad and open-ended; the working hypothesis can provide the focus.*

Specific Aim 1:	Specific Aim 2:	Specific Aim 3:
Working Hypothesis:	Working Hypothesis:	Working Hypothesis:

How

Expected Outcomes: *What your aims are likely to produce, how that would contribute to the overall objective, and what broader impact this would have on this area of research.*

- The *expected outcomes* are …

Broader Impact

- The *broader impact* is…

Payoff

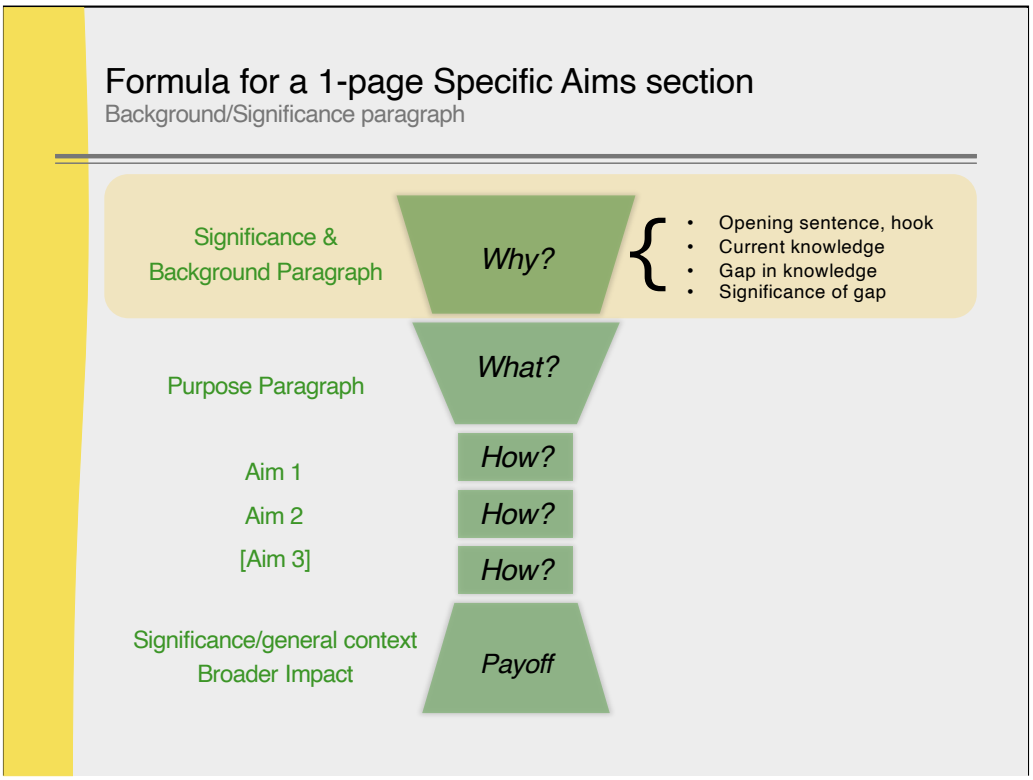
Adapted in part from The Grant Application Writer's Workbook by Stephen Russell and David Morrison

Scientific Editing and Research Communication Core (SERCC) | The University of Iowa Roy J and Lucille A Carver College of Medicine
COM-ScientificEditing@uiowa.edu | https://medicine.uiowa.edu/sercc/resources

Updates available at: https://medicine.uiowa.edu/sercc/resources/writing-grants

Do this as a bullet outline first

This is one of our Specific Aims page templates



- Opening sentence: immediately establish relevance of the proposal to agency mission
- Current knowledge: enough background for the reader to follow why the gap is important = why your study will be significant.
    - Do not go off on a tangent that will distract the reader
- Gap in knowledge – key to logic of whole page
    - everything downstream must be consistent with it
    - Should not go on tangents that stray from addressing this gap
- The significance of this gap – vertical vs lateral change

    Vertical change — e.g. how something works

    Lateral change — how a known process works in another cell line, incremental

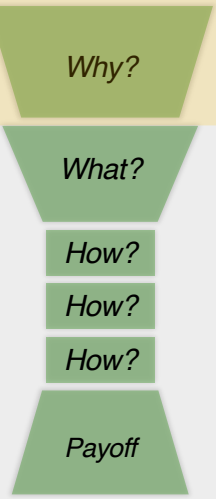
Formula for a 1-page Specific Aims section

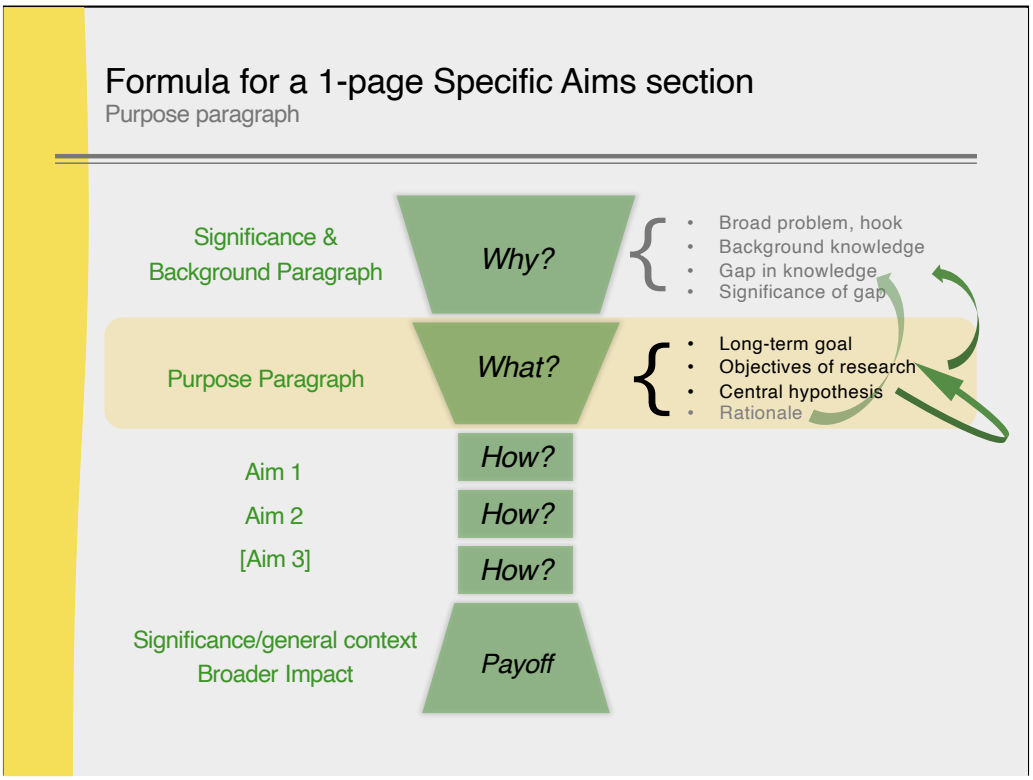
Background/Significance paragraph

Significance &
Background Paragraph

Reviewers should

- understand why your research area is relevant to agency's mission
- be up to speed with state of knowledge in the field
- understand the gap in the knowledge base, and that it is an important problem





Long-term goal is most important for:

- Faculty, especially ESIs applying for R grants
- Faculty and post-docs applying for K awards

- Must reflect an area of research pursued by your laboratory
- NIH likes projects with the potential for RENEWAL

Objectives of the proposed research: (clear goal that addresses gap)

- Define purpose of proposed project (filling gap/unmet need)
- Must be achievable in allotted time
- If you have a long-term goal, this must be a logical next step toward achieving it (linkage must be obvious)
- Must have a defined endpoint (not simply "to study process x")
  - otherwise, when would you be done?
  - overemphasizes process, rather than product, of research

Central hypothesis – provide focus for your grant application

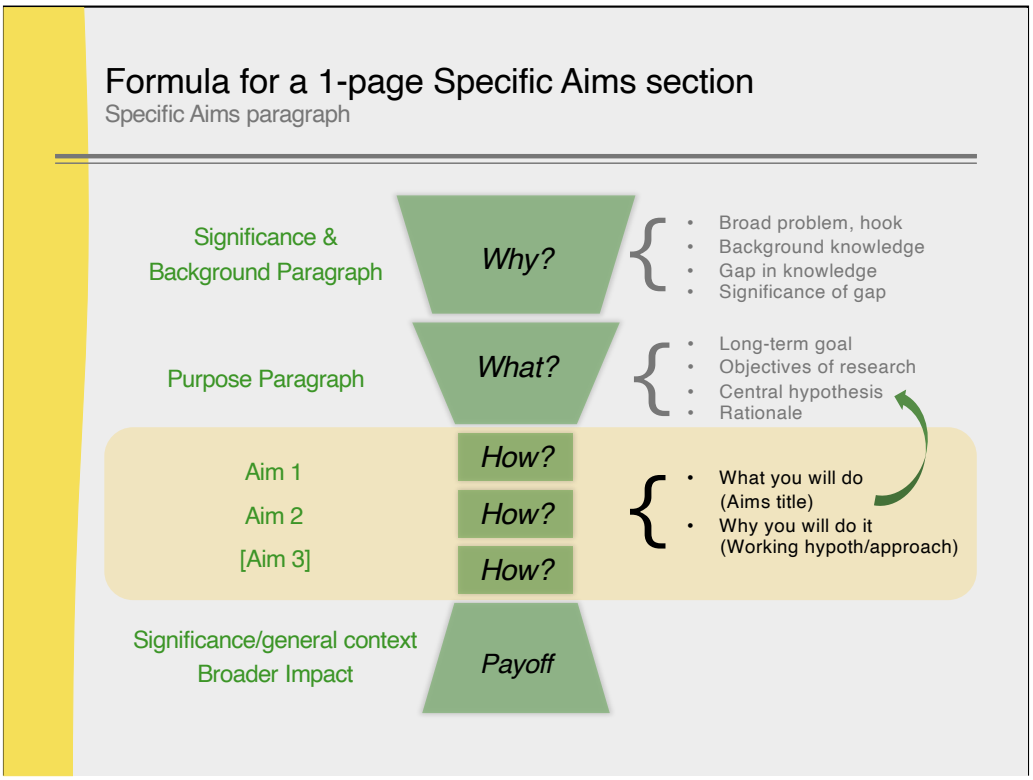
- Must link to objective
- Must give direction to project => the best bet for accomplishing objective
- Must be objectively testable (no predetermined conclusion)
- Should have components that are individually testable (by aims)
- *If application addresses a need, provide best bet as to how to meet the need*

What hypothesis is based on – PD? Literature?

- Can be easier to state hypothesis before justifying it so that reviewers can fit data into pre-established framework

Rationale – why you want to undertake this research, e.g., what will become possible that is not now

- Must link back to gap identified in first paragraph – whose resolution will allow you to take the important next step
- An opportunity to excite the reviewers!
- The challenge: to deliver this exciting message without repeating of the "gap as a problem" verbatim



Headlines (aims titles):

- Purpose: attract a reviewer's attention/capture their interest
- Must link back to some part of your central hypothesis
  - (If unmet-need based application, describe what will be done.)
- Should not be descriptive* (focused on what is being done)
  - do not use characterize/correlate/describe" if you have a hypothesis
- Should be broad and open-ended

Formula for a 1-page Specific Aims section

Specific Aims paragraph

Specific Aims titles

- Should be broad and open-ended

Specific Aim 2: Determine whether mapped CEC loci influence CCT.

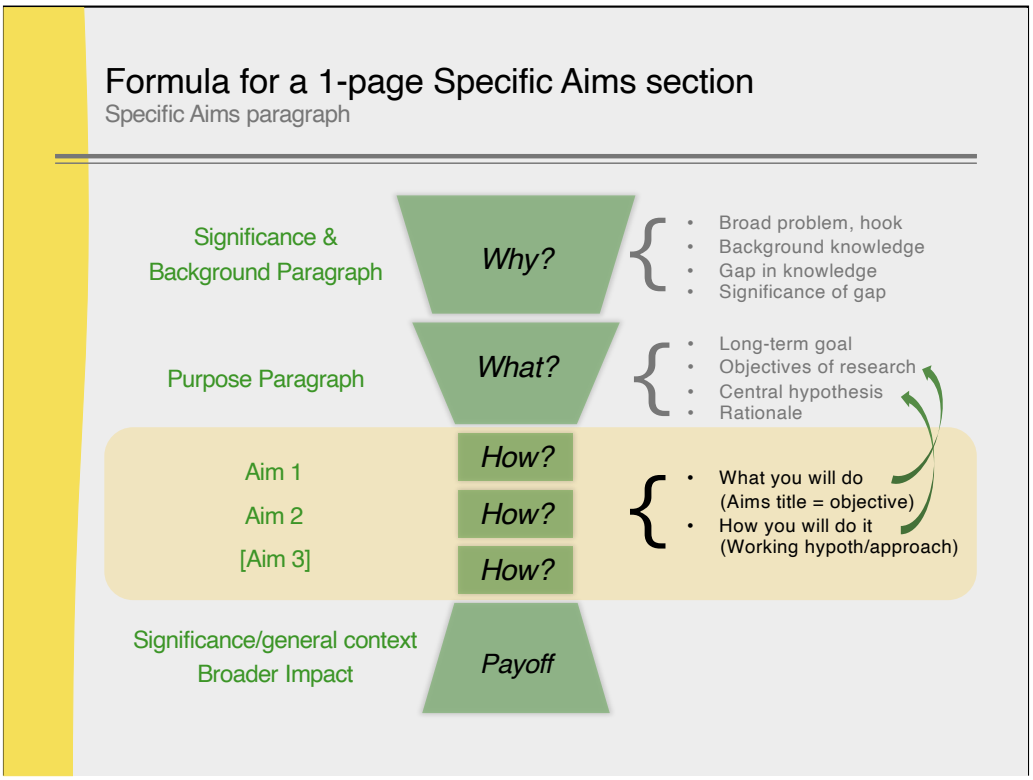
Specific Aim 2: Determine the extent to which the mapped CEC loci influence CCT.

If you don't know that CEC loci have an influence, broaden the scope of the aim

Specific Aim 2: Identify factors that influence CCT.

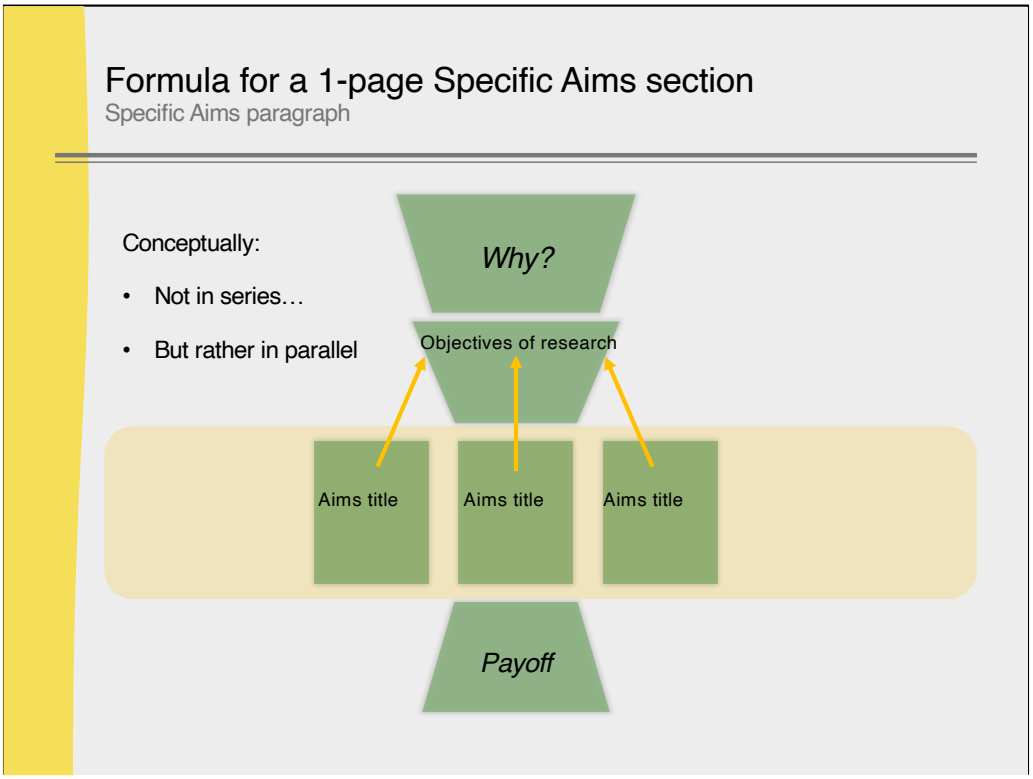
* In the case of unmet-need based applications, the aims will describe what will be done.

- What's the problem if you use this as a title?

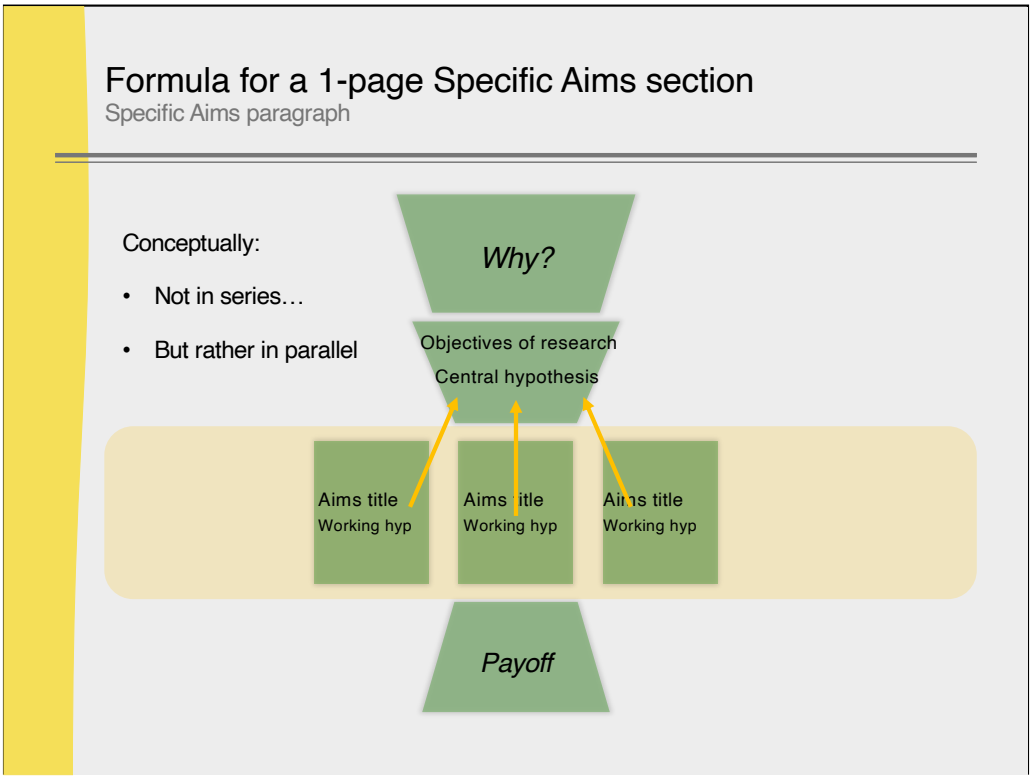


Working hypothesis:

- Purpose: to focus / provide direction for the aim
- If you only have space for the working hypothesis, be sure to write it so that it's clear what kind of approach you'll use.
- Ideally, you would add another sentence or two to spell this out, do so.
- Like the central hypothesis, this is ideally based on preliminary data (to justify focus on this vs. all other possibilities*)
- * **IF space allows**, briefly indicate a general approach after the working hypothesis
- OVERALL, the aim should be consistent with the objective(s) of the proposed research



- Each Aims title should reflect a component of the objective of the proposed research.



- Each working hypothesis should reflect a component of the central hypothesis.

Formula for a 1-page Specific Aims section

Specific Aims paragraph

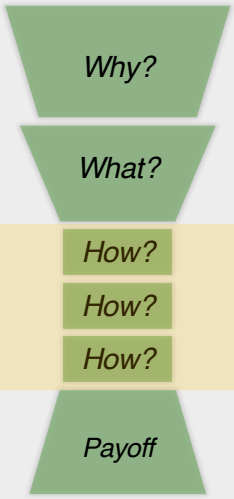
Reviewers should understand

- What specific goals you plan to achieve
- How aims relate to overall objective and hypothesis

Aim 1

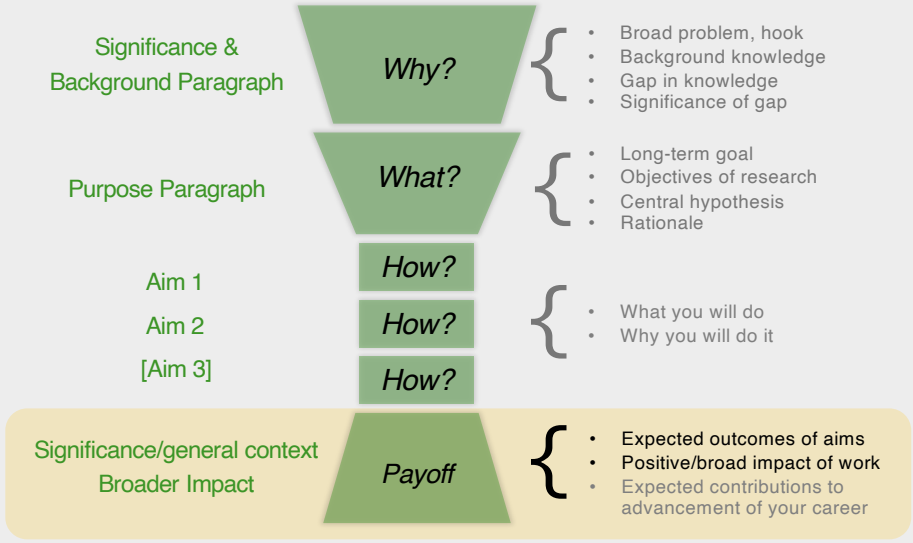
Aim 2

[Aim 3]



Formula for a 1-page Specific Aims section

Impact paragraph

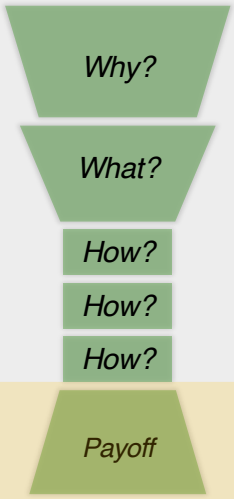


Formula for a 1-page Specific Aims section

Impact paragraph

Reviewers should:

- know what return they can expect if they recommend funding of your application
- will hopefully be inspired to advocate your project



Significance/general context

Broader Impact

Summary:

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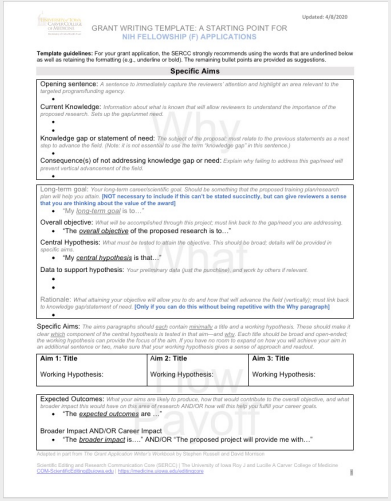


GRANT WRITING TEMPLATE: A STARTING POINT FOR NIH FELLOWSHIP (F) APPLICATIONS

Updated: 4/8/2020

Template guidelines: For your grant application, the SERCC strongly recommends using the words that are underlined below as well as retaining the formatting (e.g., underline or bold). The remaining bullet points are provided as suggestions.

Specific Aims

Opening sentence: *A sentence to immediately capture the reviewers' attention and highlight an area relevant to the targeted program/funding agency.*

Current Knowledge: *Information about what is known that will allow reviewers to understand the importance of the proposed research. Sets up the gap/unmet need.*

Knowledge gap or statement of need: *The subject of the proposal must relate to the previous statements as a next step to advance the field. (Note: it is not essential to use the term "knowledge gap" in this sentence.)*

Consequence(s) of not addressing knowledge gap or need: *Explain why failing to address this gap/need will prevent vertical advancement of the field.*

Long-term goal: *Your long-term career/scientific goal. Should be something that the proposed training plan/research plan will help you attain.* **[NOT necessary to include if this can't be stated succinctly, but can give reviewers a sense that you are thinking about the value of the award]**
- "My long-term goal is to…"

Overall objective: *What will be accomplished through this project; must link back to the gap/need you are addressing.*
- "The overall objective of the proposed research is to…"

Central Hypothesis: *What must be tested to attain the objective. This should be broad; details will be provided in specific aims.*
- "My central hypothesis is that…"

Data to support hypothesis: *Your preliminary data (pull the punchlines), and work by others if relevant.*

Rationale: *What attaining your objective will allow you to do and how that will advance the field (vertically); must link back to knowledge gap/statement of need.* **[Only if you can do this without being repetitive with the Why paragraph]**

Specific Aims: *The aims paragraphs should each contain minimally: a title and a working hypothesis. These should make it clear which component of the central hypothesis is tested in that aim—and why. Each title should be broad and open-ended; the working hypothesis can provide the focus of the aim. If you have no room to expand on how you will achieve your aim in an additional sentence or two, make sure that your working hypothesis gives a sense of approach and readout.*

Aim 1: Title	Aim 2: Title	Aim 3: Title
Working Hypothesis:	Working Hypothesis:	Working Hypothesis:

Expected Outcomes: *What your aims are likely to produce, how that would contribute to the overall objective, and what broader impact this would have on this area of research AND/OR how will this help you fulfill your career goals.*
- "The expected outcomes are …"

Broader Impact AND/OR Career Impact
- "The broader impact is…." AND/OR "The proposed project will provide me with…"

Adapted in part from The Grant Application Writer's Workbook by Stephen Russell and David Morrison

Scientific Editing and Research Communication Core (SERCC) | The University of Iowa Roy J and Lucille A Carver College of Medicine
CCNA OpenBioEditingResources.org | https://medicine.uiowa.edu/sercc/resources

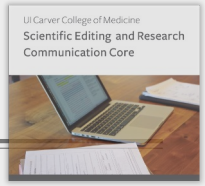
Why
What
How
How
How
Payoff

- ***Why?***
  - Broad problem, hook
  - Background knowledge
  - Gap in knowledge
  - Significance of gap
- ***What?***
  - Long-term goal
  - Objectives of research
  - Central hypothesis
  - Rationale
- ***How?***
- ***How?***
  - What you will do
  - Why you will do it
- ***How?***
- ***Payoff***
  - Expected outcomes of aims
  - Positive/broad impact of work
  - Expected contributions to advancement of your career

https://medicine.uiowa.edu/sercc/resources/writing-grants

- Here's a summary – showing the general principles of going from broad to narrow – culminating in what you will do
- Any questions so far?

Moving beyond the bullet points



Start with an outline of bullet points (based on template)

- Take a break before starting to expand the outline into sentences and paragraphs
- Seek constructive criticism from colleagues
  - Does each component serve its purpose?
  - Does each component link to the others in the right way?
  - Is the progression of the logic linear?
- Try to represent Specific Aims in a figure
  - Should be simple
  - Should illustrate relationships among aims
  - Even if it isn't used on the Specific Aims page it can solidify your thinking and convey concepts

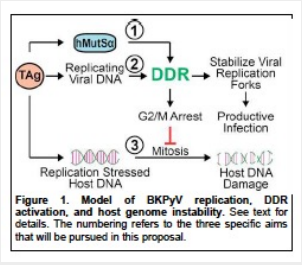
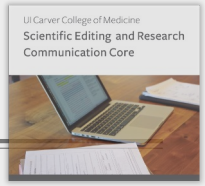


Figure 1. Model of BKPyV replication, DDR activation, and host genome instability. See text for details. The numbering refers to the three specific aims that will be pursued in this proposal.

Example from Mengxi Jiang, NIH R01 funded in 2015, posted on Open Grants https://grants.nih.gov/reproducibility/index.htm

Final thoughts on Specific Aims page:



- Leave nothing to interpretation of reviewers (spell out meaning)
- *Italicize* or *italicize and underline* key words
  - don't overdo (frequency, style)
- Minimize number of citations in this section (maximally linchpin references)
- Talking about outcomes:
  - Do not overstate (we will discover/prove)
  - Do not understate (may lay the foundation for; may be relevant to)
  - Make it conditional (has the potential to; is expected to identify)

Highligting must me meaningful and not overly complicated!

Research Strategy…

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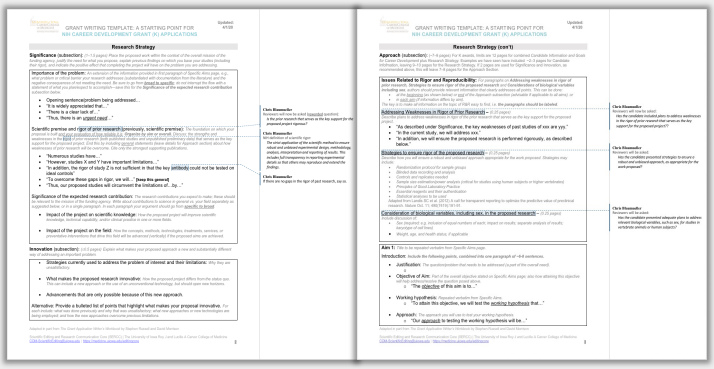
Scientific Editing and Research Communication Core

- Significance Section
- Innovation Section
- Approach



https://medicine.uiowa.edu/sercc/resources/writing-grants

- Before moving on to Rigor in RS, will just talk briefly about Innovation section

Innovation Section…

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Innovation (subsection): *(≤0.5 pages) Explain what makes your proposed approach a new and substantially different way of addressing an important problem.*

- Strategies currently used to address the problem of interest and their limitations: *Why they are unsatisfactory.*
- What makes the proposed research innovative: *How the proposed project differs from the status quo. This can include a new approach or the use of an unconventional technology, but should open new horizons.*
- Advancements that are only possible because of this new approach.

Alternative: Provide a bulleted list of points that highlight what makes your proposal innovative. *For each include: what was done previously and why that was unsatisfactory; what new approaches or new technologies are being employed; and how the new approaches overcome previous limitations.*

Limit to 0.5 pages

- Explain what makes your proposed approach a new and substantially different way of addressing an important problem
- For every aspect of innovation you discuss (ideally, limit to 1–3)
  - Current strategies and their limitations.
  - What makes the proposed research innovative: new approach? use of unconventional technology?
  - Advances that are only possible because of this new approach.

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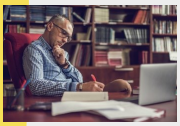
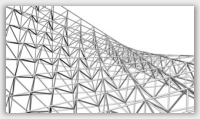
Topics



Grants:
Mechanisms and Review at NIH

Grantsmanship:
Structuring the Specific Aims Page

Considerations for the Innovation Section



Grantsmanship and Rigor/Reproducibility:

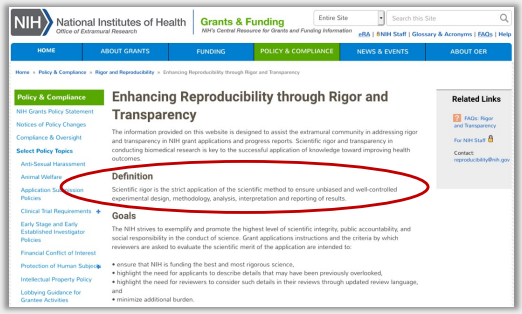
The Significance Section

The Approach Section

Resources

NIH definition of Scientific Rigor (2018)…

- *the strict application of the scientific method*
- *to ensure unbiased and well-controlled*
  - *— experimental design*
  - *— methodology*
  - *— analysis*
  - *— interpretation and*
  - *— reporting*
- *of results*



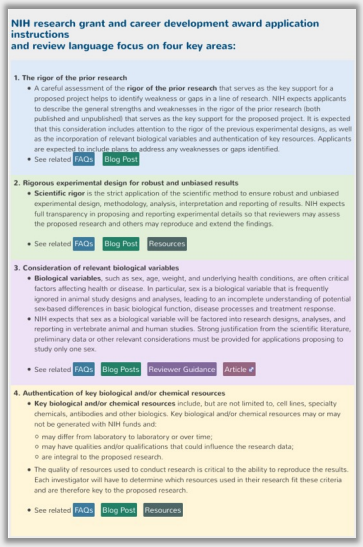
https://grants.nih.gov/policy/reproducibility/index.htm

Posted 11/27/18

In 2018, the NIH made serious efforts to address the problem that some researchers were building proposals on poor previous research and poor experimental design.

- What does "Scientific Rigor" mean to the NIH? What do they want you to pay attention to?
  - Studies on which ideas are based are sound experimentally.
  - Study design is sound
  - Results proposed will be interpretable
  - Will account for potential differences in outcomes due to factors like sex, weight, age...
  - Samples used will actually be what the authors think they are

Current NIH Instructions



NIH research grant and career development award application instructions and review language focus on four key areas:

1. The rigor of the prior research
- A careful assessment of the **rigor of the prior research** that serves as the key support for a proposed project helps to identify weakness or gaps in a line of research. NIH expects applicants to describe the general strengths and weaknesses in the rigor of the prior research (both published and unpublished) that serves as the key support for the proposed project. It is expected that this consideration includes attention to the rigor of the previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources. Applicants are expected to include plans to address any weaknesses or gaps identified.
- See related FAQs Blog Post

2. Rigorous experimental design for robust and unbiased results
- **Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. NIH expects full transparency in proposing and reporting experimental details so that reviewers may assess the proposed research and others may reproduce and extend the findings.
- See related FAQs Blog Post Resources

3. Consideration of relevant biological variables
- **Biological variables**, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response.
- 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.
- See related FAQs Blog Posts Reviewer Guidance Article

4. Authentication of key biological and/or chemical resources
- **Key biological and/or chemical resources** include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Key biological and/or chemical resources may or may not be generated with NIH funds and:
  - may differ from laboratory to laboratory or over time;
  - may have qualities and/or qualifications that could influence the research data;
  - are integral to the proposed research.
- The quality of resources used to conduct research is critical to the ability to reproduce the results. Each investigator will have to determine which resources used in their research fit these criteria and are therefore key to the proposed research.
- See related FAQs Blog Post Resources

Rigor: prior research

Rigor: proposed research

Relevant biological variables

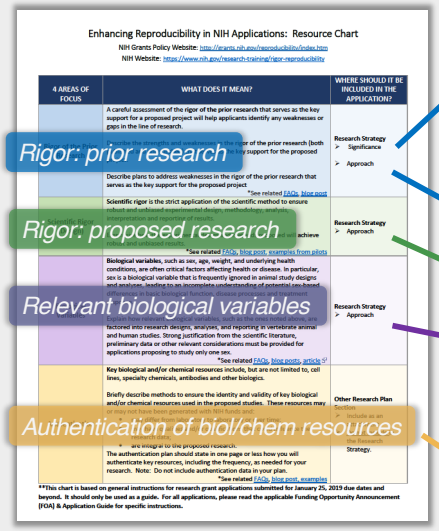
Authentication of biol/chem resources

https://grants.nih.gov/policy/reproducibility/guidance.htm
Updated November 26, 2018

Current NIH instructions related to Rigor and Reproducibility

- Here is what they want you to pay attention to in ALL grant types

Where is each addressed?



Significance section

- Weaknesses in rigor of ***prior research***

Approach section

- How weaknesses in rigor of ***prior research*** will be addressed
- How rigor of ***proposed research*** will be ensured
- Consideration of biological variables, including sex, in the proposed research

Ancillary Document

- Resource authentication

https://grants.nih.gov/policy/reproducibility/guidance.htm; Updated November 26, 2018

Where does this go?

Here this is mapped to another NIH resource (this is going to get messy…)

- We ask ourselves – is the required information in the right places (***many times – no***)
- Staff of the Division of Sponsored Program DSP ask too, especially for ancillary documents

Addressed in grant writing templates…

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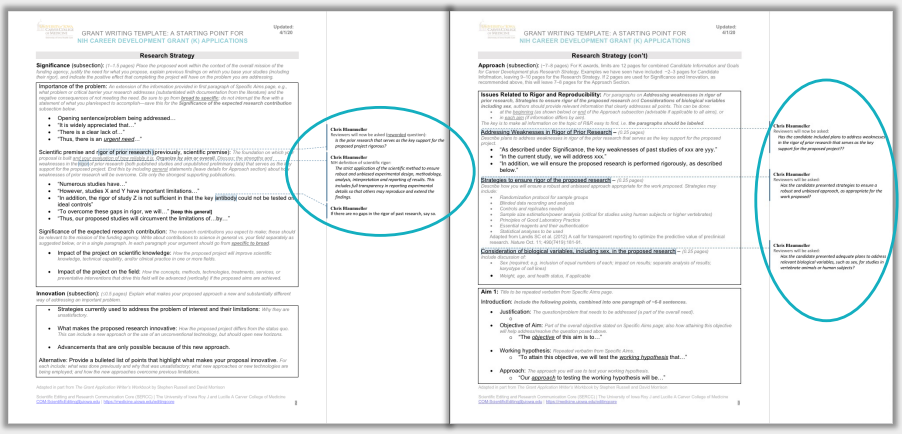

https://medicine.uiowa.edu/sercc/resources/writing-grants

- Our writing templates address these requirements in both the Significance and Approach sections

Reviewer questions for Significance section

1) Does the project address an important problem or a critical barrier to progress in the field?
2) Is the prior research that serves as the key support for the proposed project rigorous?
3) If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
4) How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Going back to the review questions for standard R, K, and F grants FOA (turn into bullet list)

- Have turned scoring criteria into headings
- These are all pretty much included for R, K, and F grants.

Significance Section…

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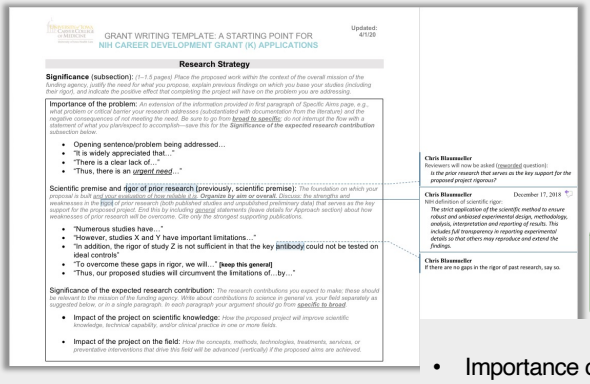


GRANT WRITING TEMPLATE: A STARTING POINT FOR NIH CAREER DEVELOPMENT GRANT (K) APPLICATIONS

Updated: 4/1/20

Research Strategy

Significance (subsection): *(1–1.5 pages) Place the proposed work within the context of the overall mission of the funding agency, justify the need for what you propose, explain previous findings on which you base your studies (including their rigor), and indicate the positive effect that completing the project will have on the problem you are addressing.*

Importance of the problem: *An extension of the information provided in first paragraph of Specific Aims page, e.g., what problem or critical barrier your research addresses (substantiated with documentation from the literature) and the negative consequences of not meeting the need. Be sure to go from broad to specific; do not interrupt the flow with a statement of what you plan/expect to accomplish—save this for the* ***Significance of the expected research contribution*** *subsection below.*

- Opening sentence/problem being addressed…
- "It is widely appreciated that…"
- "There is a clear lack of…"
- "Thus, there is an urgent need…"

Scientific premise and rigor of prior research (previously, scientific premise): *The foundation on which your proposal is built and Less exhaustive of how reliably it is. Organize by aim or overall. Discuss the strengths and weaknesses in the rigor of prior research (both published studies and unpublished preliminary data) that serves as the key support for the proposed project. End this by including general statements (leave details for Approach section) about how weaknesses of prior research will be overcome. Cite only the strongest supporting publications.*

- "Numerous studies have…"
- "However, studies X and Y have important limitations…"
- "In addition, the rigor of study Z is not sufficient in that the key antibody could not be tested on ideal controls"
- "To overcome these gaps in rigor, we will…" **[keep this general]**
- "Thus, our proposed studies will circumvent the limitations of…by…"

Significance of the expected research contribution: *The research contributions you expect to make; these should be relevant to the mission of the funding agency. Write about contributions to science in general vs. your field separately as suggested below, or in a single paragraph. In each paragraph your argument should go from specific to broad.*

- **Impact of the project on scientific knowledge:** *How the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more fields.*
- **Impact of the project on the field:** *How the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be advanced (vertically if the proposed aims are achieved.*

Chris Blaumueller
Reviewers will now be asked (rewarded question):
Is the prior research that serves as the key support for the proposed project rigorous?

Chris Blaumueller December 17, 2018
Nih definition of scientific rigor:
The strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. This includes full transparency in reporting experimental details so that others may reproduce and extend the findings.

Chris Blaumueller
If there are no gaps in the rigor of past research, say so.

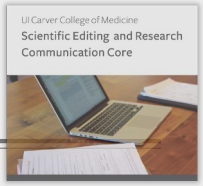
Limit to
- 1.5 pp in 12-p grant
- 1.0 p in 6-p grant

- Importance of problem
- Scientific premise and Rigor of Prior Research
- Significance of Expected Research Contribution
  - Impact on Scientific Knowledge
  - Impact on the Field

https://medicine.uiowa.edu/sercc/resources/writing-grants

- Again, summarized in the template
- Avoid making this too long
  - At most, provide the data for 1 or 2 experiments that are the linchpins of the scientific premise.
  - Other supporting data for premise and for feasibility should be presented under Approach.

What does “rigor of prior research” apply to?



Importance of the problem and/or critical barriers to progress

Scientific premise* and rigor of the prior research

Significance of the expected research contribution

- Impact of the project on scientific knowledge / technical capability / clinical practice
- Impact of the project on the field

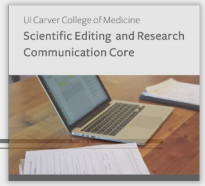
* The relevant literature: Strengths and weaknesses
- Rigor of study design (e.g. statistical power, blinded analysis)
- Incorporation of relevant biological variables (e.g. detail regarding sex)

Your preliminary data that contribute to scientific foundation of proposal.

What does rigor apply to?

- The literature
- Your preliminary data

How this might be worded

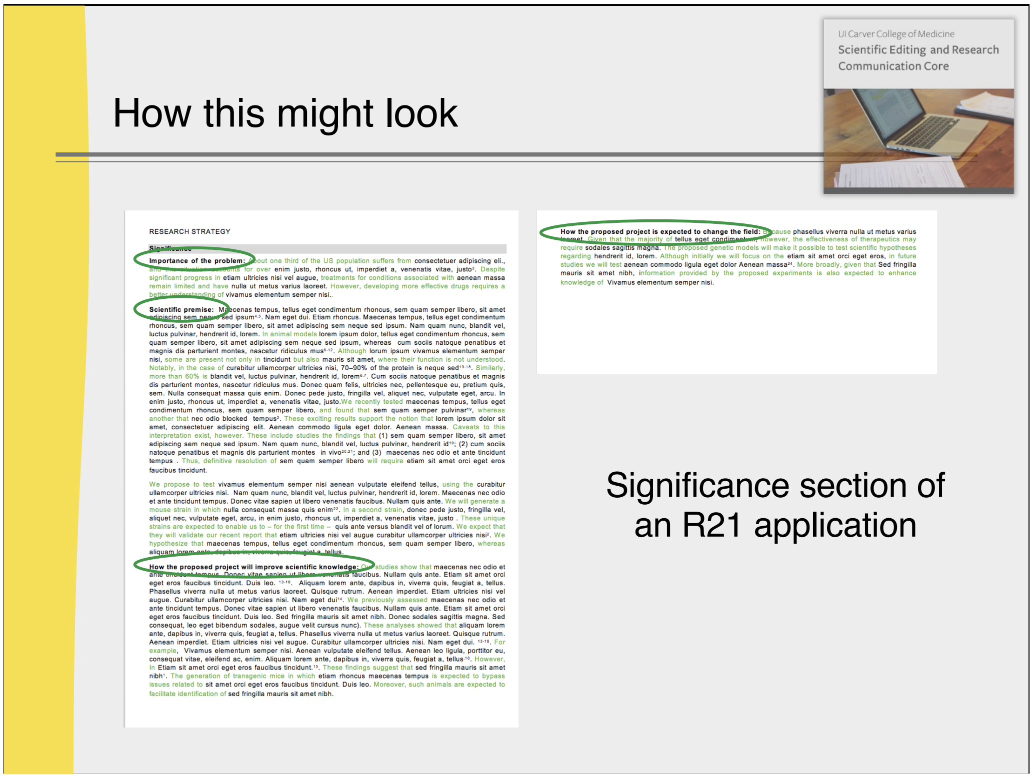


1) Importance of the problem and/or critical barriers to progress
2) Scientific premise and rigor of the prior research (organize overall or by aim)*
   - Numerous studies have…
   - However, studies X and Y have important limitations…
   - In addition, the rigor of study Z was not sufficient in that…
   - To overcome these gaps in rigor, we will… [keep this general here]
   - Thus, our proposed studies will circumvent the limitations of… by …
3) Significance of the expected research contribution
   - Impact of the project on scientific knowledge / technical capability / clinical practice
   - Impact of the project on the field

If there was a lack of rigor and it's possible to discuss diplomatically…

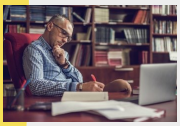
Specifically mention limitations ... good lead-in for innovation

- Thoughts on what to include and how to say it!
- Trick is to do this well without alienating potential reviewers



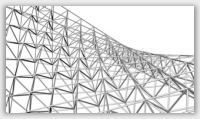
An example of this layout (but with just SP) – still works well

Topics



Grants:
Mechanisms and Review at NIH

Grantsmanship:
Structuring the Specific Aims Page
Considerations for the Innovation Section



Grantsmanship and Rigor/Reproducibility:

The Significance Section
The Approach Section

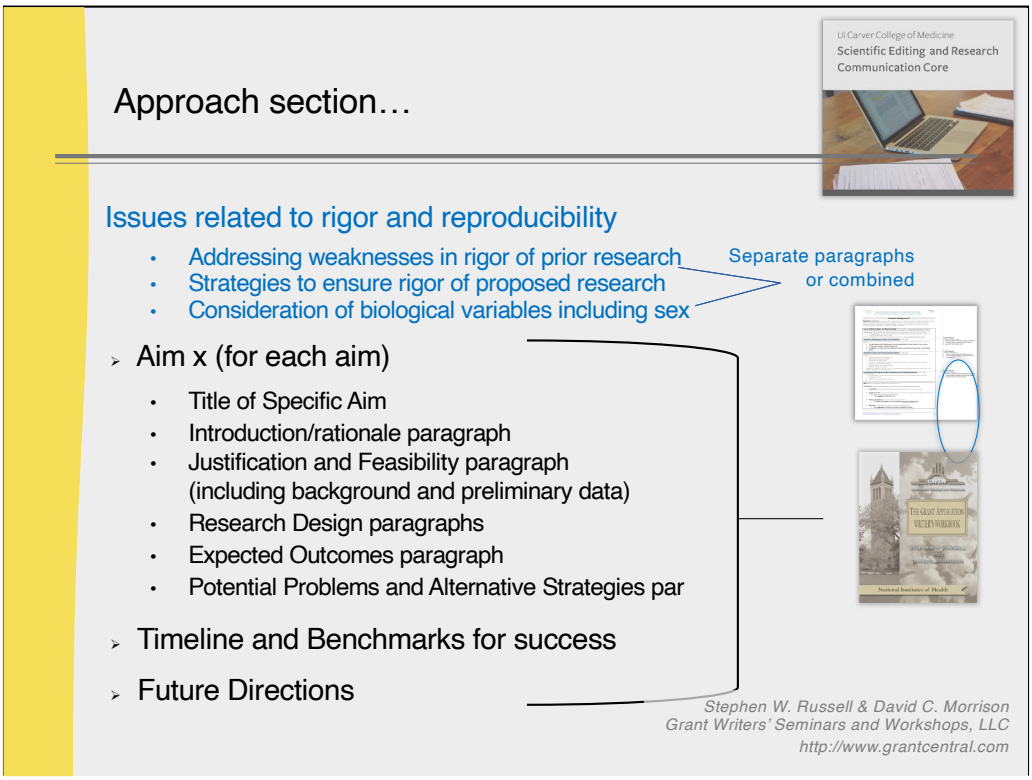
Resources

Reviewer questions for Approach section

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Have the investigators presented strategies to ensure *a robust and unbiased approach*, as appropriate for the work proposed? (2016)
- Have the investigators included plans to *address weaknesses in the rigor of prior research* that serves as the key support for the proposed project? (2018)
- Are potential problems, alternative strategies, and benchmarks for success presented?
- If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
- Have the investigators presented *adequate plans to address relevant biological variables*, such as sex, for studies in vertebrate animals or human subjects? (2016)
- If the project involves human subjects and/or NIH-defined clinical research, are the plans for: protections for human subjects, and inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, …?

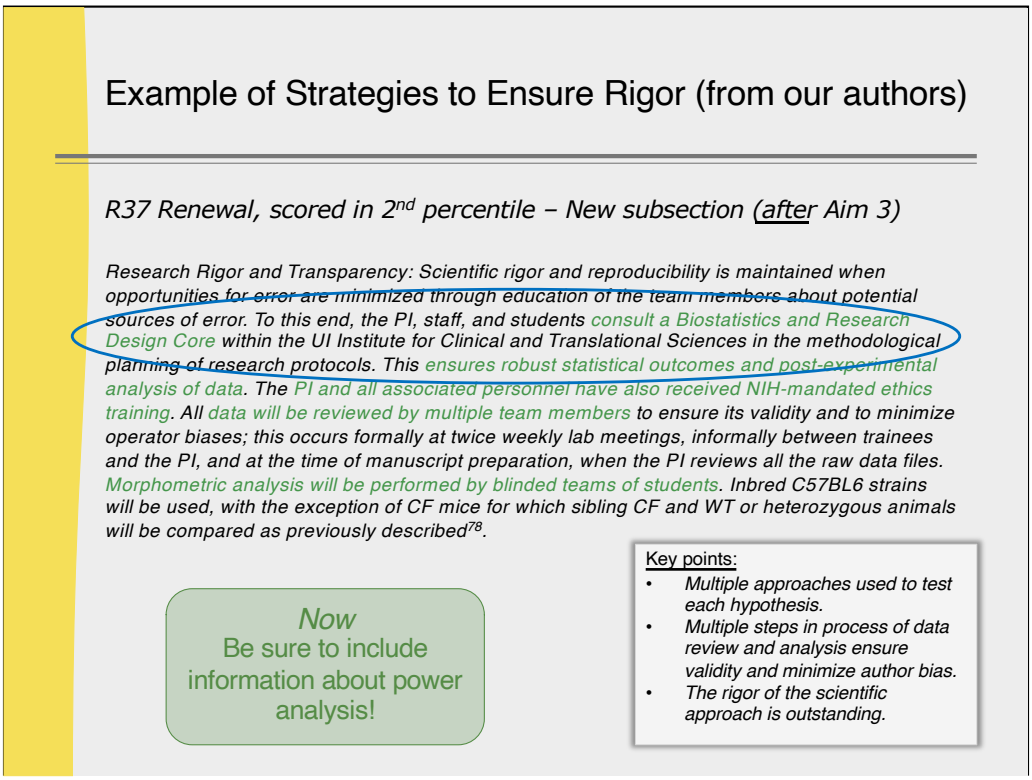
Moving on to Approach:

- These are the current review criteria
- We've built our recommendations for this on the old Grant Writers' model for this section



Here is our favorite suggestion

- Can work in strategies for ensuring rigor and SABV into aims if that's a better fit for your story (e.g., different aims require very different approaches)
- Make it part of Research Design
- For Justification and Feasibility
    - Remind reader of any PD in Significance, provide any additional support here
    - Tell reader about feasibility data
- Expected outcomes and alternative stratiegies – recommend doing by aim rather than subaims
- Timeline and Future directions are their own major headers = to Aims
    - Don't make them look like they're part of Aim 2 or 3 (final aim)



Note that we've moved beyond this – be sure to include the power analysis information

- even if you don't have it now, explain why not and how you'll do it.

Examples of Strategies to Ensure Rigor (posted by NIH)

- *Excerpts from awarded applications reviewed under a pilot FOA for rigorous experimental design … this is only one part of updated instruction and review language.*
- *Selected based on high overall impact scores and positive reviewer comments specific to rigor.*
- *Provided to show how elements of rigor and transparency have been succinctly provided in applications; they may not represent all of the aspects/may still have room for improvement.*
- *May be updated as applications are reviewed and awarded under the revised rigor and transparency review.*

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].

Key points:

- *Number of groups, allocation random, age, why that age.*
- *Dosage, number of doses administered*
- *Route of administration, contingency*
- *Group size, power*
- *Blinding, of whom*
- *Experience*

Rigor and Reproducibility
https://grants.nih.gov/reproducibility/index.htm

Examples of Strategies to Ensure Rigor (posted by NIH)

Example 2:

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.

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.

Key points:

Aim 1

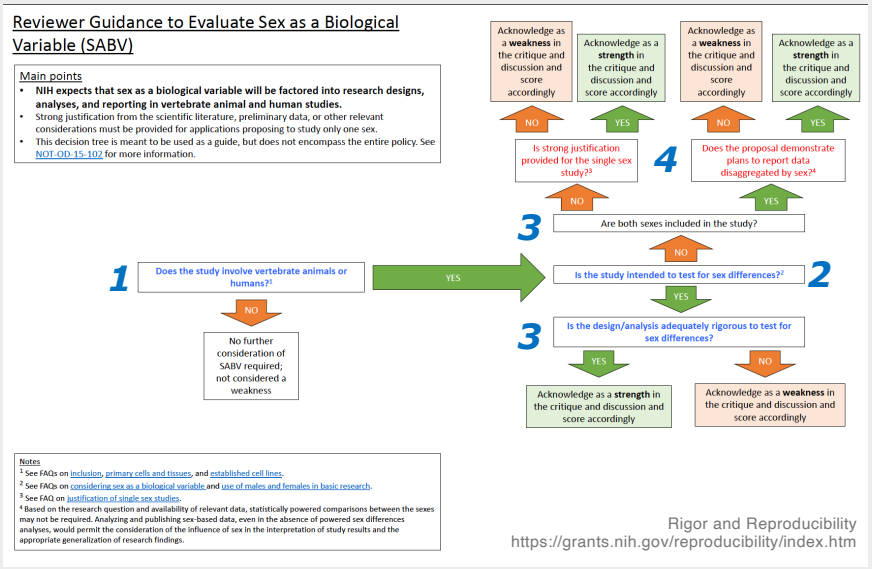
- Brief summary of overall approach
- Number of replicates, same/ different dates, reporting of average with standard deviation
- Types of statistical analysis

Aim 2

- Blinding, solubilization of test and control compounds
- Random assignments
- Who will analyze
- Power analysis; number of animals per group
- Number of animals, contingency

Rigor and Reproducibility https://grants.nih.gov/reproducibility/index.htm

Consideration of Sex as a Biological Variable (SABV)



- Flow chart from NIH to figure out whether you need to consider sex as a biological variable in your study.
  - Does the study involve vertebrate animals? humans?
  - Y: Is the study intended to test of sex differences?
    - Y: Is the design/analysis adequately rigorous to test for them?
      - Y: STRENGTH
      - N: Weakness
    - N: Are both sexes included in the study?
      - Y: Will data be reported disaggregated by sex? ...
      - N: Is strong justification provided for not including both? ...
      - ADDRESS this even if it seems obvious that only one sex is needed!

Example of Consideration of SABV

"Recent" (2016) example including SABV – New subsection (before Aim 1)

Methods to achieve robust and unbiased results:
... and WT littermate controls were generated as described in Fig. 1. These lines were genotyped and cataloged across 10 backcrosses into the C57BL/6J strain. Only animals that are of the same genetic background and handled in the same way will be compared. Congenic Xxxx KO mice (B6.129P2-Xxxx^{zzzz}/J; stock #xxxx) were obtained from Jackson Laboratories. These mice had been backcrossed with C57BL/6J animals >30 generations. For cultures of dissociated PFC cells obtained from neonates, there is no reason to think that gender differences exist; hence male and female pups will be randomly allocated to experimental groups at P1. For the experiments involving [brain] slices from P30 animals, samples will be prepared from equal numbers of age-matched male and female animals and results will be tracked by gender. Each experiment will be performed in triplicate and repeated at least three times. Dose-response and time-course analyses will be conducted for each compound to ensure that the responses are maximal. We have extensive experience with blinded analysis, treatment paradigms, and group analyses[e.g.50-55]. The Co-Investigator has extensive experience in establishing LTP and LTP-D paradigms in both rats and mice[44,45]. Experimental designs are rigorously vetted including, at a minimum, testing of only a priori hypotheses and blinding for subjective ratings. Except as noted, biological and chemical resources will be obtained from standard commercial suppliers; effects of novel agents are documented in the literature. Data will be analyzed using ANOVA followed by posthoc testing with Student's t-test.

NO

YES

Great example of project that we had:

- some data for which sex was **not** going to be a concern
- and some data for which sex was a concern and how they would deal with it

- Key points:
  - Dealt with both (did not ignore the one where sex is not relevant)
  - It's not good enough just to gather data from both sexes
  - Must also track and analyze by sex, at least in a first round

Key: Explain your thinking

Timeline at end of the Approach section…

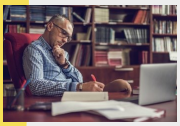
Inclusion of a well organized timeline…

- Quickly illustrates how realistic the proposal is
- Can pre-empt concerns about interdependence of aims

Table 5: Timeline for the proposed research plan					
	Year 1	Year 2	Year 3	Year 4	Year 5
Aim 1.1	X	X			
Aim 1.2		X	X		
Aim 1.3				X	X
Aim 1.4	X	X	X	X	X
Aim 2.1	X	X			
Aim 2.2			X	X	X

This table illustrates that the aims are not dependent on one another!

Topics



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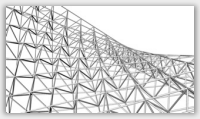


Grantsmanship and Rigor/Reproducibility:

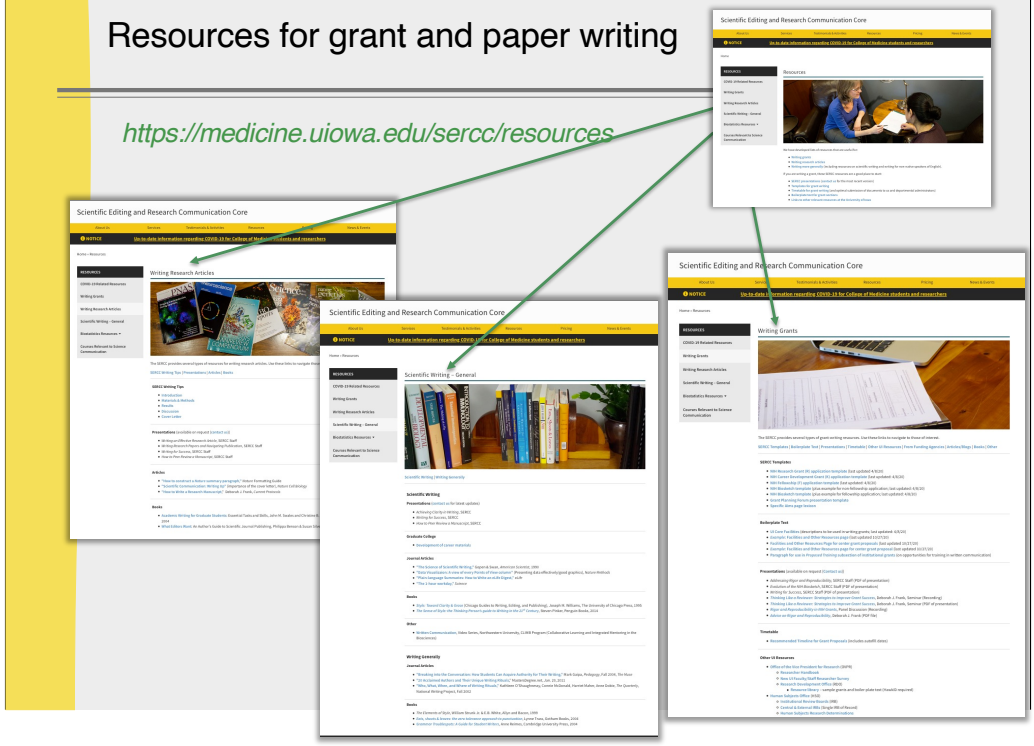
The Significance Section

The Approach Section

Resources

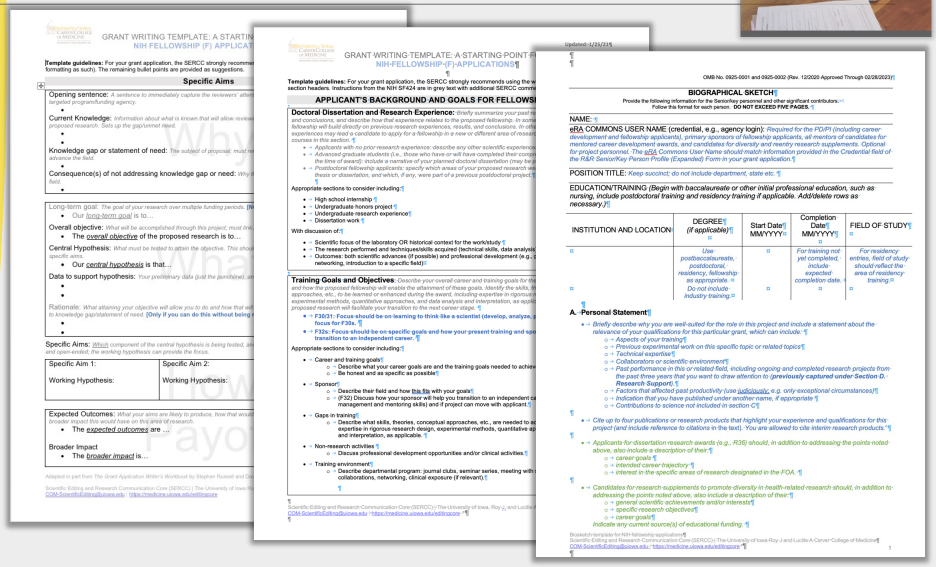
Resources for grant and paper writing

https://medicine.uiowa.edu/sercc/resources



For grant writing…

UI Carver College of Medicine
Scientific Editing and Research Communication Core



Updates available at: https://medicine.uiowa.edu/sercc/resources/writing-grants

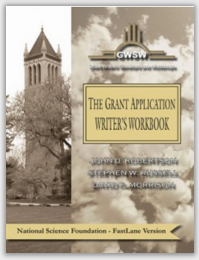
For grant writing…

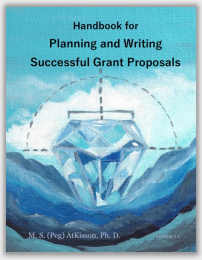
John Robertson, Stephen Russell, And David Morrison

Writing Winning Grants (NIH, NSF…)

Grant Writers' Seminars and Workshops, LLC

http://www.grantcentral.com





AtKisson Training Group

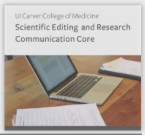
https://www.atkissontraininggroup.com/resources

Our templates for R and K grants are

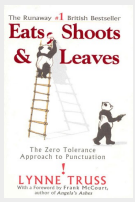
- Based in part on these resources

NOTE: CLARITY of BIG-PICTURE matters a lot.

For writing generally:

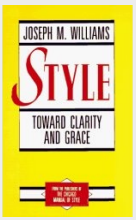


William Strunk Jr. & E.B. White
The elements of style
(Fourth Edition)
Allyn and Bacon, 1999



Lynne Truss
Eats, shoots & leaves:
the zero tolerance approach to punctuation
Gotham Books
2004

Joseph M. Williams
Style: Toward Clarity & Grace
(Chicago Guides to Writing, Editing, and Publishing)
The University of Chicago Press
1995



George Gopen & Judith Swan
The Science of Scientific Writing
American Scientist 78, 550-558, 1990
https://www.americanscientist.org/blog/the-long-view/the-science-of-scientific-writing

Writing tips by Gary Westbrook & Linda Cooper
Society for Neuroscience and *The Journal of Neuroscience* websites
https://www.coursehero.com/file/12969603/Tech-for-Clear-Scientific-Writing-Cooper/

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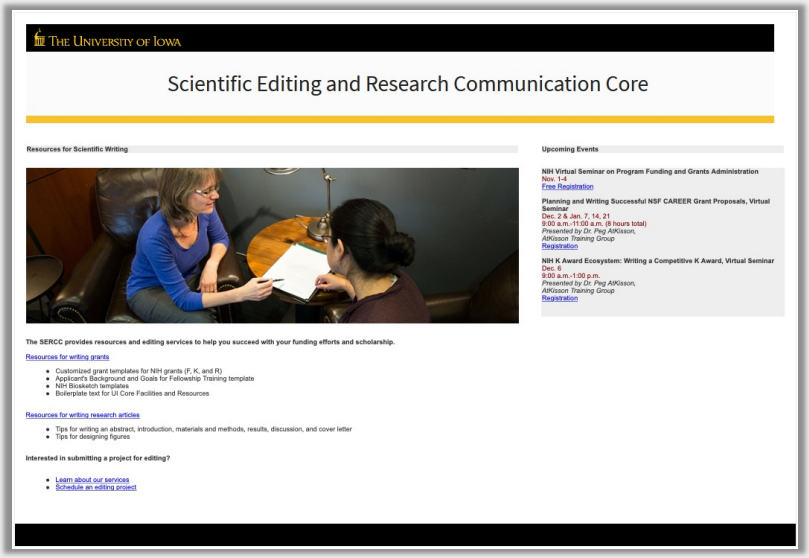
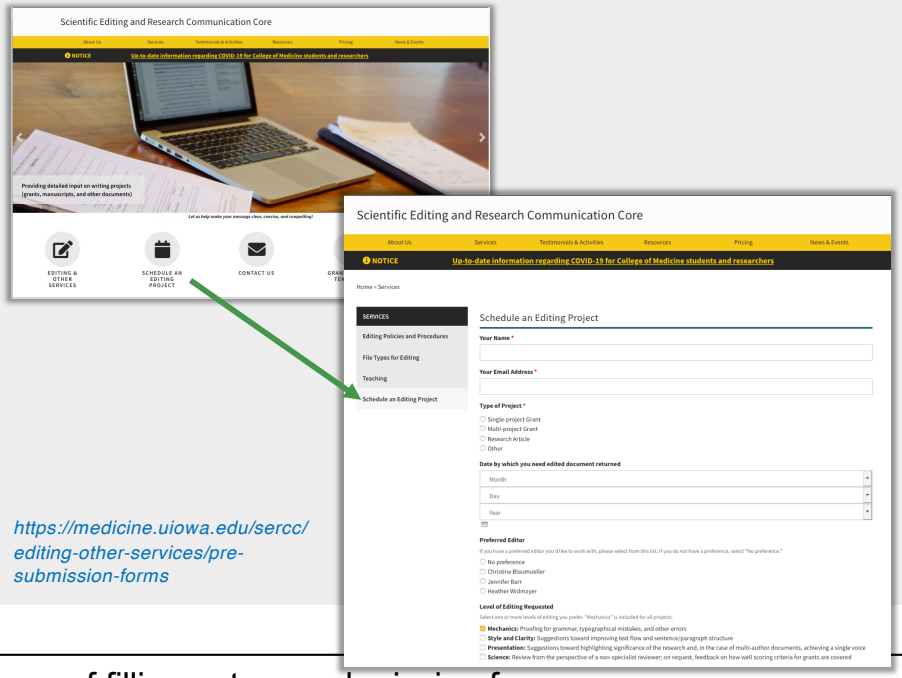


https://medicine.uiowa.edu/sercc/content/subscribe-sercc-listserv

Planning for Submission

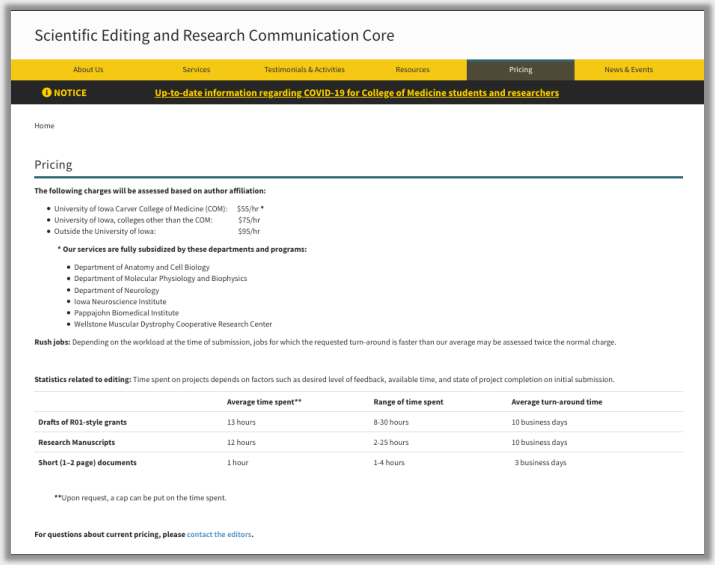


https://medicine.uiowa.edu/sercc/editing-other-services/pre-submission-forms

Advantages of filling out pre-submission form:

- it is helpful if people fill these out so we have advanced notice of projects that might come in, especially given how busy we are at times
- We can try to get your project done faster if you're already in line! (must give a reasonable window for this to work)
- We get all the information we need right away (e.g. title, MFK) and won't have to follow up

Pricing



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The following charges will be assessed based on author affiliation:

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- University of Iowa, colleges other than the COM: $75/hr
- Outside the University of Iowa: $95/hr

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- Department of Neurology
- Iowa Neuroscience Institute
- Pappajohn Biomedical Institute
- Wellstone Muscular Dystrophy Cooperative Research Center

Rush jobs: Depending on the workload at the time of submission, jobs for which the requested turn-around is faster than our average may be assessed twice the normal charge.

Statistics related to editing: Time spent on projects depends on factors such as desired level of feedback, available time, and state of project completion on initial submission.

	Average time spent**	Range of time spent	Average turn-around time
Drafts of R01-style grants	13 hours	8-30 hours	10 business days
Research Manuscripts	12 hours	2-25 hours	10 business days
Short (1–2 page) documents	1 hour	1-4 hours	3 business days

**Upon request, a cap can be put on the time spent.

For questions about current pricing, please contact the editors.

https://medicine.uiowa.edu/sercc/pricing-1

Make your grant stand out…

- Follow instructions
- Make all necessary information easy to find
- Make the text inviting
- Tell a story
- Make sure your meaning is clear – to others

Questions?

How to make your grant stand out

- Follow instructions
- Use headers
- Use headers that include words from the NIH solicitation (make it easy for reviewers find what they need/when they need it)
- Include white space
- Make sure your meaning is clear – get feedback from close colleagues and from colleagues outside your field