

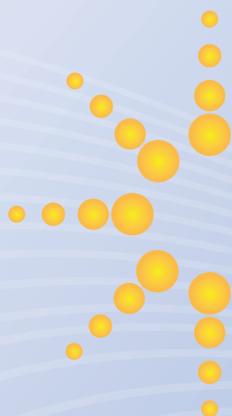
5th Edition

Forms Version D

NIH R01

Grant Application Mentor

An Educational How-to Manual



Principal
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Association™

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Best Regards,

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Color Key:

Throughout this report, we have used highlighted text to indicate the following:

 — original text by authors of this report
(no color)

 — directly quoted NIH information
(pink)

 — paraphrased NIH information
(yellow)

 — directly quoted information from successful NIH grant applications
(blue)

Introduction

Applying for a National Institutes of Health (NIH) R01 grant is an involved process with many facets to consider and extensive guidelines to follow. This manual will guide you through the steps involved and help you submit the best proposal possible.

Of course, all research begins with an idea, and you must determine if yours should be funded by an R01 grant. Your research must meet NIH's priorities, but it is just as essential that the grant is the appropriate mechanism for your project.

Once you've verified that an R01 is right for you, you'll need to work out the specifics. Think about when to apply, what to title your proposal, and how to articulate your hypothesis. But before you actually begin, consider creating a writing schedule. Chapter 1 includes a sample timetable that will help you move through the steps of the application process more easily and manage your time effectively.

As you begin writing your proposal, remember the message you are trying to convey. You should explain your project thoroughly so readers will understand all aspects of it. But you also want to tell a compelling story and entice reviewers to approve your research.

Several chapters of this manual help guide you through the writing process. They offer advice for developing your Project Summary/Abstract, Biographical Sketch, Environment section and Research Plan. They also help you ensure your Research Strategy addresses your project's Innovation, Significance, Approach and Overall Impact.

When considering your project costs, refer to our chapter on creating a budget. You may also need to consult the section detailing considerations for special agents and human and animal subjects. Each chapter includes checks to ensure you're following NIH guidelines every step along the way.

Before you submit your application, take time to review it. Make certain you've included all the necessary components and adhered to all rules. You'll also need to correct any errors and remedy weaknesses before sending your proposal to NIH.

Once you've submitted your application, it goes through a comprehensive review. The final chapter of this manual delineates that process. It also explains what NIH scores mean and what steps you can take after you receive them.

Chapter 1: Starting the Grant Application Process

Before you can begin filling in your National Institutes of Health (NIH) grant application, there are several steps you must take first. For instance, you have to define the research project idea for which you are seeking funding. This may seem rather obvious, but the process for doing so is anything but simple.

You will also have to determine whether your research project will even qualify for an NIH grant, and several factors influence that determination.

Then — before you write a single word of your application — you should map out a strategy for it, which can include the following:

- Determining if the R01 grant mechanism is right for you.
- Picking a research project that you feel passionate about, yet which meets NIH funding priorities at the same time.
- Choosing people with expertise and experience who can advise you as you work on your application.

Next, you will need to more clearly define your proposed research project. NIH has specific criteria for investigators it will support, and there are explicit concepts every grant application must include to be considered. For instance, how you formulate your project title and hypothesis can significantly influence your research's fundability.

Finally, you should develop a writing schedule to ensure that your grant application meets NIH's submission deadlines. There are several possible tactics that you may use to help you.

Now, let's walk through each of the steps.

QUALIFYING FOR AN NIH GRANT

You may have an amazing research idea that will shake the very roots of the scientific world, but if it does not meet the requirements set out by the NIH and its Institutes, Centers and Offices (ICOs), your application will not get past the initial review.

First, every application topic must be consistent with the NIH mission statement:

“NIH’s mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability.”

The goals of the agency are:

- to foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health;
- to develop, maintain, and renew scientific human and physical resources that will ensure the Nation's capability to prevent disease;
- to expand the knowledge base in medical and associated sciences in order to enhance the Nation's economic well-being and ensure a continued high return on the public investment in research; and
- to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

In realizing these goals, the NIH provides leadership and direction to programs designed to improve the health of the Nation by conducting and supporting research:

- in the causes, diagnosis, prevention, and cure of human diseases;
- in the processes of human growth and development;
- in the biological effects of environmental contaminants;
- in the understanding of mental, addictive and physical disorders; and
- in directing programs for the collection, dissemination, and exchange of information in medicine and health, including the development and support of medical libraries and the training of medical librarians and other health information specialists.

What this means:

The agency states that its goals include the following:

- Foster fundamental creative discoveries, innovative research strategies and their applications as a basis for ultimately protecting and improving health;
- Develop, maintain, and review scientific human and physical resources that will ensure the nation’s capability to prevent disease;
- Expand the knowledge base in medical and associated sciences to enhance the nation’s economic well-being and ensure a continued high return on the public investment in research; and
- Exemplify and promote the highest level of scientific integrity, public accountability and social responsibility in the conduct of science.

As a result, NIH indicates that it will conduct and support research in the following areas:

- Causes, diagnosis, prevention and cure of human diseases;
- Processes of human growth and development;
- Biological effects of environmental contaminants;
- Understanding of mental, addictive and physical disorders; and
- Directing programs for the collection, dissemination and exchange of information in medicine and health, including development and support of medical libraries and the training of medical librarians and other health information specialists.

On the other hand, the agency would not fund projects like the following:

- Devising strategies to conserve water resources;
- Projects related to environmental pollution but unrelated to human health, such as floating plastic debris in the ocean or carbon dioxide absorption by concrete; and
- Research regarding dynamic water processes as they affect climate and environmental change.



TIP:

Review NIH’s qualifying elements and compare them to your proposed research idea to make sure they match up before you move forward with your grant application.

Consequently, your initial step must be to review the above qualifying elements and compare them to your proposed research idea. If there is a good match, then you should move forward with your grant application.

If your proposed research does not meet NIH mission or other requirements, however, you should consider seeking a grant award from another source, such as the National Science Foundation (NSF). For example, NIH might fund computer-modeling research that seeks to predict the structure of cellular proteins and the spread or containment of infectious diseases, such as avian flu. Whereas NSF-sponsored research in math and computer modeling more likely would be used to design a concert hall, simulate weather patterns and assemble an investment portfolio that reduces risk and maximizes reward.

Institutes, Centers and Offices (ICOs) Also Weigh in

Next, you must consider that NIH is made up of 27 semiautonomous ICOs. And each of these has its own defined research focus.

The NIH's Center for Scientific Review (CSR) staff performs the initial review of your grant application before assigning it to one of its review panels called Study Sections, which are organized around specific scientific subject matter. Nonetheless, you can suggest that a specific Study Section review your application, even though the CSR has the final decision.

Of the 27 ICOs, the following accept R01 grant applications for investigator-initiated research proposals:

National Cancer Institute (NCI, www.cancer.gov) — Through basic and clinical biomedical research and training, the NCI conducts and supports research regarding cancer prevention and/or manageability, early-stage identification, innovative treatment development.

National Eye Institute (NEI, www.nei.nih.gov) — NEI conducts and supports research that seeks to prevent and treat eye diseases and other vision disorders, including sight-saving treatments, visual impairment and blindness reduction, and quality-of-life improvements.

National Heart, Lung and Blood Institute (NHLBI, www.nhlbi.nih.gov) — NHLBI backs grants centered on treating diseases of the heart, blood vessels, lungs and blood; blood resources; and sleep disorders.

National Human Genome Research Institute (NHGRI, www.genome.gov) — Devoted to advancing health through genome research, the NHGRI supports research aimed at expanding understanding of human biology and improving human health.

National Institute on Aging (NIA, www.nia.nih.gov) — The NIA leads a national research program regarding the biomedical, social and behavioral aspects of the aging process; age-related disease and disability prevention; and a better quality of life for older Americans.

National Institute on Alcohol Abuse and Alcoholism (NIAAA, www.niaaa.nih.gov) — NIAAA focuses on research to improve the treatment and prevention of alcoholism and alcohol-related problems.

National Institute of Allergy and Infectious Diseases (NIAID, www.niaid.nih.gov) — NIAID's research centers on understanding, treating, and preventing infectious, immunologic, and allergic diseases.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS, www.niams.nih.gov) — NIAMS supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; as well as basic and clinical scientist training to carry out this research.

National Institute of Biomedical Imaging and Bioengineering (NIBIB, www.nibib.nih.gov) — NIBIB promotes fundamental discoveries, design, and development, and translation and assessment of technological capabilities in biomedical imaging and bioengineering, enabled by relevant areas of information science, physics, chemistry, mathematics, materials science and computer sciences.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD, www.nichd.nih.gov) — The NICHD supports child-

centered research regarding fertility, pregnancy, growth, development and medical rehabilitation.

National Institute on Deafness and Other Communication Diseases (NIDCD, www.nidcd.nih.gov) — The NIDCD conducts and supports biomedical research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech and language.

National Institute of Dental and Craniofacial Research (NIDCR, www.nidcr.nih.gov) — NIDCR leads national research to understand, treat, and prevent infectious and inherited craniofacial-oral-dental diseases and disorders.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, www2.niddk.nih.gov) — NIDDK conducts and supports basic and applied research regarding diabetes, endocrinology and metabolic diseases; digestive diseases and nutrition; and kidney, urologic and hematologic diseases.

National Institute on Drug Abuse (NIDA, www.nida.nih.gov) — NIDA's funding efforts focus on research across several disciplines to improve drug abuse and addiction prevention, treatment and policy.

National Institute of Environmental Health Sciences (NIEHS, www.niehs.nih.gov) — NIEHS seeks to define how environmental exposures, genetic susceptibility and age interact to affect an individual's health.

National Institute of General Medical Sciences (NIGMS, www.nigms.nih.gov) — The NIGMS supports basic biomedical research that is not targeted to specific diseases. NIGMS funds studies on genes, proteins and cells, as well as on fundamental processes like communication with and between cells, how our bodies use energy and how we respond to medicines. NIGMS also supports research training programs for biomedical scientists and has special programs to encourage underrepresented minorities to pursue biomedical research careers.

National Institute of Mental Health (NIMH, www.nimh.nih.gov) — NIMH is dedicated to understanding, treating and preventing mental illnesses through basic research on the brain and behavior, and through clinical, epidemiological and services research.

National Institute on Minority Health and Health Disparities (NIMHD, www.nimhd.nih.gov) — NIMHD mission is to lead scientific research to improve minority health and eliminate health disparities by evaluating all minority health and health disparities research and activities of the NIH while supporting research in minority health and health disparities.

National Institute of Neurological Disorders and Stroke (NINDS, www.ninds.nih.gov) — NINDS’s mission is to support and conduct research, both basic and clinical, on the normal and diseased nervous system, foster investigators’ training in the basic and clinical neurosciences, and seek better understanding, diagnosis, treatment and prevention of neurological disorders.

National Institute on Nursing Research (NINR, www.ninr.nih.gov) — NINR awards grants for clinical and basic research to establish a scientific basis for individual patient care, including patient management during illness and recovery; risk reduction for disease and disability; promoting healthy lifestyles and quality of life for those with chronic illness; and caring for those at the end of life. This research may also include families within a community context, and may focus on the special needs of at-risk and underserved populations, emphasizing health disparities.

National Library of Medicine (NLM, www.nlm.nih.gov) — NLM conducts and supports research in biomedical communications and provides grant for training, medical library resources, and biomedical informatics and communications research.

National Center for Complementary and Integrative Health (NCCIH, <https://nccih.nih.gov/>) —NCCIH defines, through rigorous scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care.

Now, let’s look at how your particular research idea might fit into one of these ICO’s coverage areas.



STRATEGY:

You can specifically request, using the Assignment Request Form in Forms-D, that your application be forwarded to a particular ICO for consideration. And you can contact institutional program officers at each ICO for direction.

For example, if your proposal involves a potential new treatment for uterine cancer, you would not look to the NINDS or NIDDK for funding opportunities. Instead, a logical first step would be to examine possible grants sponsored by the NCI. And if you are submitting a request for an R01 grant, you can specifically request that your application be forwarded to the NCI for consideration using the Assignment Request Form in Forms-D.

Alternatively, if your research centers on asthma triggers in older adults, you would likely request that NIAID review your grant application.

One tactic for selecting which ICO(s) might be the best fit is to contact specific institutional program officers — frequently called POs — to assess their level of enthusiasm for your research and how it might fit into any initiatives that group might be considering. If you feel your proposal could fall under more than one ICO, you can contact POs at each institute for direction.

How do you find a relevant PO for your proposal? Once you have selected the ICO(s) that best fit with your proposed research, go to that group's Web site. Once there, you can review the staff directory to locate the appropriate PO. For example, on the NIAID site you can click on "Finding People" within the left hand side toolbar. You can also locate POs within FOAs, the eRA Commons or your Notice of Award.

When you speak with the PO you have identified, you can request details regarding possible topics for investigator-initiated research, such as the following:

- New scientific directions and opportunities, including published concepts (for example, NIAID posts its Concepts: Potential Opportunities on its Web site, www.niaid.nih.gov).
- Unpublished high-priority topics.

One way to approach this conversation is to schedule it beforehand and write a brief, one-page or less lay explanation of your research and submit it to the PO. This will prevent you from wasting meeting time trying to explain the finer points of your proposal. This meeting is also a great time to make a friend of your PO, making sure to consider any offered advice seriously.

Your Institution Must Qualify for NIH Support as Well

In addition to your research qualifying for NIH support, your host institution must also qualify.

In fact, NIH actually awards most grant types — including R01 grants — to the institution rather than to the individual applying for the grant. Universities, small and large businesses, and foreign institutions are among those that qualify for R01 grants.

On the other hand, NIH limits the eligibility for other types of grants. For instance, foreign institutions may not apply for small business awards such as an SBIR grant. Similarly, most federal organizations may receive NIH grants, but those in the Public Health Services may get NIH funds only under exceptional circumstances.

Keep in mind that although NIH grants primarily go to domestic institutions, you do not need U.S. citizenship or affiliation to become a principal investigator for most grant types, including R01. You, however, must have U.S. citizenship for a small business award, and you must be a U.S. citizen or a permanent resident — that is, have an Alien Registration Card — for fellowships, career development awards (with one minor exception) and training grants.

NIH also outlines the following requirements for foreign principal investigators working on NIH-funded grants:

- If you are not a U.S. citizen but working at a U.S. institution, you must remain there long enough to finish your project.
 - If you do not have a permanent visa, state in your application that your visa will allow you to remain in the United States long enough to be productive on the project.
 - Your institution must ensure that you have an appropriate visa.
- Persons from countries listed as State Sponsors of Terrorism cannot work with any agent covered by the USA Patriot Act.

Additionally, when a foreign institution submits an application, NIH requires additional steps to register for electronic application.



REMEMBER:

NIH actually awards most grant types — including R01 grants — to the institution rather than to the individual applying for the grant.

Qualifying for an R01 NIH Grant

NIH supports scientists at various stages in their careers, from pre-doctoral fellowships to investigators with extensive experience who run large research centers. Nonetheless, the agency — as well as some of its ICOs — does have minimal eligibility requirements for most research grants, including the R01.

Here are NIH's criteria if you are seeking an independent research grant, such as an R01:

- Hold an advanced degree appropriate to the research (in most fields, you likely would need a Ph.D. or M.D.)
- Within your institution, hold a position or rank that allows you to apply for such grants (often assistant professor or higher).
- Have a publication or patent record or a history of high-level research supervision in the field in which you are applying.
- Work in a research institution that has the resources — meaning equipment and lab space — you will need.

You must show the NIH peer reviewers that you can handle leading a major research project. That means your grant application must clearly demonstrate your expert qualifications, your institute's commitment to you and your project, and the independent space you will have by the time NIH or one of its ICOs makes the award.

If you find that you do not meet NIH's R01 qualifications, the agency offers other funding mechanisms that might be more appropriate and prepare you substantially for your first R01 opportunity. These can take the form of a Pathway to Independence Award or New Innovator Award.

MAP OUT YOUR PLAN

Understand that from the start that the grant application process takes a good deal of time. Generally, experts recommend that you should plan to spend roughly two months or longer preparing your R01 application. And if your research will require human or animal subjects, the preparation time could increase as much as six months.

Even if your application flies through the review process on the first try and is approved for funding, you likely will not see a penny of the award for another six to 18 months.

Reviewers, however, may not approve an application on its first pass through the process. And even with approval, you may not receive funding for your proposal, depending on the amount of money available for approved applications.

And because NIH funds approximately 17 percent of the R01 and R01 equivalent applications it receives, and most applicants must revise and resubmit their proposals. This means your award might not be forthcoming for as long as 28 months from the time you initially apply until you potentially receive funding based on your resubmission.

Therefore, having a game plan for your application is a must.

Nail Down Your Strategy

The average NIH grant lasts three to five years. Consequently, one grant will not fund your life's work as a researcher.

As a result, you should look further down the road in your career. One option is to plan your research goals for a longer period — for instance, the next 10 years. Then you can divide your goals into segments that you can accomplish in three to five years.

Suppose, for example, you choose to study methicillin-resistant *Staphylococcus aureus* (MRSA). This is a broad topic, so you break your research into three grant topics, each covering three years:

1. The contribution of gene regulation to DNA mutation, insertion, deletion and rearrangement in MRSA.



TIP:

Experts recommend that you plan to spend roughly two months or longer preparing your R01 application.

2. The transfer of genes between *Staphylococcus aureus* strains that allow them to become methicillin-resistant.
3. How to determine the specific genetic requirements that allow *Staphylococcus aureus* to become methicillin-resistant.

This particular approach has three advantages:

- It keeps your research projects small and manageable. When applying for a grant, you should propose an amount of work that you can do within the time and resources you request. New investigators, in particular, frequently propose too much in one application, and reviewers may reject their proposals merely because there is an unreasonable amount of work involved.
- It forces you to consider your research in terms of maintaining your career, which helps you to avoid the common pitfall of failing to get a renewal for your project.
- This type of big-picture planning helps to keep you focused on your main idea, as well as how you will pursue it for several years of funding.

Make Sure the R01 Is the Right Mechanism for You

As part of your grant application strategy, you must determine whether the R01 grant mechanism is right for your proposed area of research. As a first step, you should speak with your identified PO and with experienced investigators in your institution for their guidance. Another resource likely will be your institution's sponsored research office.

NIH offers hundreds of specialized award types with varying characteristics, so if this is your first application, you should seek guidance in choosing your grant mechanism. In addition, there are other issues that only add to the complexity:

- Not all ICOs participate in all the grant activity codes. For instance, most ICOs use R01s, but there are several — such as the National Cancer Institute — that do not use R03s (for small research programs).
- Different ICOs or initiatives may have different requirements even for the same activity code. For example, AIDS-related R01 applications have different deadlines than other R01s.

- ICOs might use a certain grant type for only certain areas of science. For instance, if your research involves platform development for drug discovery, you might be required to use the R41 mechanism, which assists researchers in commercializing innovative technologies, rather than an R01.

One strategy is to speak with a relevant PO at NIH who may help you focus down on the grant mechanism that is right for your proposed research.

Specifically when requesting an R01 award, you should remember that these provide three to five years of support to researchers who have preliminary data. If you lack this, consider an exploratory/developmental research grant (R21) or a small grant (R03) that will fund such efforts. The data you thereby obtain will then support a later R01 application.



STRATEGY:

Speak with a relevant NIH PO who may help you focus down on the grant mechanism that is right for your proposed research.

CHOOSE YOUR PROJECT

There are seven points you should consider when choosing your R01 research area:

1. Pick a research topic that will allow you to make a large impact on a focused area. Your peer reviewers will examine your grant application to determine how your research will advance the scientific field. In fact, this, along with your project's feasibility, likely will be the determining factors regarding your research's fundability. The more focused your project, the less likely it will overlap with another application. Consider the following questions when selecting your topic:

- Can the research make a difference? For instance, will it open a new area of discovery or develop a new approach to a significant problem?
- Will reviewers consider your research area to have the same priority that you do? Get an unbiased opinion from a mentor or other trusted colleague.
- How will your idea stack up against NIH review criteria? We will examine these criteria in later sections of this manual.

2. Define the current gaps and opportunities in your field. Carve out your own research niche. Avoid crowded areas because making a difference will be more difficult when you have more competitors. At the same time, find an interesting challenge that you likely will be able to solve. Read the scientific literature so you understand the current state of the problem(s) you want to address and what research to avoid because it has already been accomplished. Also, brainstorm ideas with colleagues.

3. Be an expert. Perhaps obviously, you should choose a research topic within your area of expertise. Although you can recruit collaborators to fill experience gaps, you should have first-hand knowledge of the science and most of the methods related to your grant application. Reviewers expect you to be the expert in your proposed investigational area, and this must be supported in your application. Assess your strengths and how they match the requirements of potential projects.

4. Examine potential research areas at NIH. The R01 grant mechanism is for investigator-initiated research, which allows you to select the topic. But you should also review the priorities at the various ICOs to determine if your proposal fits among their stated internally or forecasted research needs.



TIP:

Write a single sentence that demonstrates how your project is well-focused, makes an impact and has a testable hypothesis.

5. Make sure your project is doable. Consider writing a single sentence that demonstrates how your project is well-focused, makes an impact and has a testable hypothesis. By limiting yourself to this format, this will help you determine if you can truly accomplish your research goals within your award period and using the level of resources that you might request. Also make sure that your science relates to the cause, diagnosis, prevention or cure of human disease — which ties it squarely to the NIH mission statement.

6. Get advice on your project's merits. Obtain the NIH PO's opinion regarding your research idea. Speak with experts at your institution and other colleagues to get their perspective concerning your proposed research's impact. Based on this input, rate the impact of your topic. If it scores poorly, refine your idea or find another topic.

7. Look at your proposed topic through a reviewer's eyes. Find the Study Sections that likely would review your area of science, and identify three or more members who would likely serve as your reviewers. Although these may not turn out to be your actual reviewers, they likely will have similar expertise to those who are. Review their published writings, and keep them in mind as you construct and review your application. This will give you an idea of the how they might assess your proposal.

Once you have worked through all seven of these points, you should be able to distill your research topic into a sufficiently focused idea that will allow you to develop your grant application more readily.



TIP:

Think of your hypothesis as the glue that holds your application together, and never force a hypothesis on experiments that are not truly hypothesis-driven.

DEFINE YOUR PROJECT

When determining what your research project will entail, follow these steps to help you stay on track:

- Create a solid, testable hypothesis
- Write a provisional title
- Decide when to apply

Creating Your Hypothesis

Most successful grant applications start with a focused, testable hypothesis, and your research design should be able to prove — or disprove — your hypothesis. In fact, your application should ask questions that test your hypothesis rather than indicate you are searching for a problem or simply collecting information.

Think of your hypothesis as the glue that holds your application together. The results of your experiments and research will ultimately determine whether your hypothesis is good science.

Also keep in mind that you should never force a hypothesis on experiments that are not truly hypothesis-driven. A statement such as, “We hypothesize that a comprehensive analysis of plasma protein in blood from patients with colon cancer will reveal the presence of unique biomarkers,” is obvious and does not add to your proposal. A better approach would be: “We hypothesize that by extending the sensitivity of mass spectrometry-based proteomics to routine detection of proteins at pg/ml concentrations with CVs less than 10 percent, we will enable the detection of low-abundance proteins that are more likely to display specificity for colon cancer.”

In addition, you should explicitly state your specific, falsifiable hypothesis. Regardless of whether you have a general, overarching one that covers the entire proposal or a specific one for each research aim, there should be a hypothesis in your application.

A vague statement such as, “We hypothesize that tumor tissues and normal tissues from the same organ will have different patterns of gene expression,” is useless. Instead, you should be more specific — for example, “We hypothesize that tumor tissue will display a gene expression profile showing elevated inflammatory responses.”

Some experts even suggest keeping your research proposal so tightly focused that you have only one hypothesis.

Research that tests a hypothesis is likely to give meaningful results, regardless of whether the data support or refute the hypothesis. NIH generally prefers grant proposals that have an impact on future research, and a testable, significant hypothesis can provide that impact.

Write a Provisional Title

The next step is writing an initial or working title to further focus your research idea and guide preparation.

Direct from NIH: The NIH Application Guide states:

Descriptive Title of Applicant’s Project

Enter a brief descriptive title of the project. This field is required.

A “new” application must have a different title from any other PHS project submitted for the same application due date with the same PD/PI. A “resubmission” or “renewal” application should normally have the same title as the previous grant or application. If the specific aims of the project have significantly changed, choose a new title.

A “revision” application must have the same title as the currently funded grant.

NIH and other PHS agencies limit title character length to 200 characters, including the spaces between words and punctuation.



REMEMBER:

NIH limits your title to 200 characters, including letters, numbers, spaces and any punctuation.

What this means:

You will finalize your title after completing your application. All reviewers will read it, so it must be informative. It may even color perception of your entire submission. At the same time, the NIH grant application limits your title to 200 characters, including letters, numbers, spaces and any punctuation.

The title is your first chance to win over reviewers with an innovative, creative idea that they will want to champion for funding. Consequently, a title that stands out from others and virtually compels reviewers to read your application gives you one more advantage.

By the way, keep in mind that — far from the niches of science — companies struggle to condense powerful advertising messages into terse phrases. For example, “Coke is it” or “A diamond is forever.” Even newspaper headline writers grapple with this challenge.

Therefore, your title is a significant piece of information that must be a unique, relevant and intriguing description of your research plan that conveys the following:

- What you will do
- How you will do it
- What the results will be

Because NIH wants to fund work that can seriously impact society and advance science, you should point to the outcome of your research in the title.

Keeping all this in mind, here are 13 tips for creating successful titles:

1. Be original and relevant. Make sure your title differs from those of already submitted applications or from funded research. NIH wants fresh, innovative projects. You can review databases of existing applications and awards at www.projectreporter.nih.gov and contact the appropriate NIH scientific review officer to ensure that your title is not redundant or closely similar to another.

2. Be accurate and use agency-friendly keywords that help officials direct your proposal to the appropriate study section. For example, using “epidemiology of” in the title will help the reviewer route the application to an epidemiology study section, such as the Neurological, Aging and Musculoskeletal Epidemiology (NAME) Study Section.

3. Find out which themes are mission-relevant, priority areas for research, or emerging as future priorities. Decision-makers at NIH seek advice from many sources when setting research priorities, including the scientific community at-large, federal advisory councils, individual researchers, professional societies, patient organizations, and voluntary health associations. Areas which continue to receive attention include cancer, HIV/AIDS, pediatric and adult obesity, and aging related topics. Recent emphasis across the NIH has been the Brain

Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, as evidenced by their announcement of its second wave of investments totaling \$85 million in fiscal year 2015 funds (<http://www.braininitiative.nih.gov/>). Since each individual IC sets its own priorities based on the input it receives, it is best to check each one for their most current areas of emphasis.

4. Use results-driven words instead of those that describe your process. For example, from funded R01 applications:

- Decrypting IGE B Cell Immunobiology
- A Systematic Analysis of Small RNA Interactions During RNA Virus Infections
- Functional Genomics Analysis Of Colonization And Persistence Of Enterococcus Faecalis In The Gastrointestinal Tract

5. Be authoritative. That means that you should let reviewers know that you know what you are talking about. For instance, if your research focuses on developing nuclear magnetic resonance methods to visualize sequence and damage-specific DNA flexibility at the atomic scale in the presence and absence of supercoiling, your grant title could be “Dynamics of Normal and Damaged DNA Under Relaxed and Supercoiled Conditions.”

6. Keep NIH criteria in mind, including significance, innovation, investigators, approach and environment. For instance, “DNA Replication Control and Its Application to Selective Killing of Cancer Cells,” can show significance, approach and innovation.

7. Use plain language. Consider the simple, direct and economical use of the words that make up this successful grant proposal title: “Public Health Preparedness and Response for Bioterrorism.” Alternatively, a wordy, awkward and dramatic way of saying the same thing might be “Will Public Health Authorities Be Ready When and If the Horrors of Bioterrorism Unfold in Their Cities?”

8. Follow the rules. As stated earlier, the NIH application limits title length to 200 characters. If yours is longer, it will be cut off at the 201st character, which could strip away the meaning and impact carried by the deleted words.

9. Use active, forward-thinking verbs, such as “defining,” “improving” or “development,” that tell readers your project points to results. For example, consider the following from awarded R01 applications:

- Defining Mechanisms and Targets in WNT Addicted Human Malignancies (PQ22)
- Improving Network Analysis and Visualization for Infectious Disease Control
- Development of Goggle System for Fluorescence Image-Guided Surgery

10. View your title as a work in progress. Your final title may differ from your initial one because a proposal’s specifics typically change during the writing process. Finalize your provisional title when you have completed the application.

11. Get input from peer scientists and individuals outside your field, preferably an English professor or an editor for proofreading and language use. Colleagues with grant-writing experience can be especially helpful.

12. If you are resubmitting, keep your proposal’s original title so that agency officials easily recognize it and look for the changes that you have made.

13. Proofread your title before you hit the “send” button. Do not rely on your spell-checking program. Instead, use a dictionary because terminology must be spelled correctly. A seemingly insignificant error could destroy your chances of winning funding.

Finally, remember that NIH uses your title — as well as your abstract — to assign your application to a study section and institute for review. The agency also uses it to report your research dollars to Congress. So your title plays a vital role not only in the review process, but also throughout the life of your research and grant.

Deciding When to Apply

NIH has three annual deadlines for submitting applications for new R01 grants: Feb. 5, June 5 and Oct. 5. For renewal R01 applications, these dates shift to March 5, July 5 and Nov. 5. And if you are submitting an AIDS or AIDS-related R01 application, there are different deadlines: Jan. 7, May 7 and Sept. 7. At the same time, if your proposal is a response to an ICO's special request for a specific research topic, the ICO can choose a special deadline at its discretion, which you can find on the ICO's Web site.

R01 Type	Grant Cycle 1 Deadline	Grant Cycle 2 Deadline	Grant Cycle 3 Deadline
New Grant Application	Feb. 5	June 5	Oct. 5
Renewal Grant Application	March 5	July 5	Nov. 5
AIDS/AIDS-related Grant Application	May 7	Sept. 7	Jan. 7

Tactically, many researchers wonder if they should target a particular deadline because the competition might not be as great at that time of year.

Officially, NIH maintains that you should submit your grant application based upon the quality of the science rather than perceived differences in funding success rates during the various grant cycles. An outstanding proposal will always attract strong consideration regardless of what time of year you submit it.

Therefore, you should submit your application as soon as your ideas are fully developed, capable of being clearly presented and well supported by convincing preliminary data.

That said, if your grant proposal scores near the percentile cutoff point for funding, timing can make a difference. But this situation does not represent a substantially better success rate.

Note: The deadlines above are accurate as of May 2016. Changes may occur, however, and you should reconfirm your various deadlines for the grant cycles relevant to your application.



REMEMBER:

NIH uses your title and abstract to report your research dollars to Congress.

CREATE A WRITING SCHEDULE

Now that you have developed a provisional title and hypothesis, you can establish a writing schedule to ensure that your application is ready to submit before one of the grant cycle deadlines.

There is a great deal of information to accumulate, digest and then integrate into your application, and this will take time. The last thing you want is to submit a grant proposal that is incomplete, sloppy or shortsighted because you ran out of time. As part of your writing schedule, consider other responsibilities that you currently have, such as teaching, lab duties, personal obligations, etc.

NIH suggests allowing at least two months for planning and writing your grant application, at least one month to get feedback on it, and then two weeks for final reviewing and proofreading before submitting it. Of course, the more complex your proposed research, the longer each stage of the process will take. Some experts even caution that preparing and writing your application can take as long as six months.

Consequently, you should set up a timetable for getting each section of the application completed and ready for review. For example:

Task	Due Date
Research field of interest to narrow research topic to manageable subject for application	
Review NIH Institutes and Centers for potential matching research focus	
Formulate hypothesis	
Create provisional title for grant proposal	
Submit hypothesis and title to colleagues for review and feedback	
Prepare Significance statement for Research Strategy section	
Prepare Innovation statement for Research Strategy section	
Outline Specific Aims section	
Etc.	

Once you have outlined your writing schedule, your last few tasks should involve assembling your application materials, having the packet reviewed by trusted colleagues (including a proofreader as well as those familiar with the science) and final submission before the deadline.

As you go through each task, do not attempt to make each section perfect on your first pass. Think of this stage as a work in progress. Once you have all the



STRATEGY:

Allow at least two months for planning and writing your grant application, at least one month to get feedback on it, and then two weeks for final reviewing and proofreading before submitting it.

application sections completed in this rough-draft format, you can review the entire package as a whole, editing and rewriting to make sure that the sections flow more coherently. Then submit it in final form.

CONCLUSION

Once you have worked through the planning stages to clearly define your research project, choose your team, formulate your title and hypothesis, and develop your writing schedule, you will have laid the groundwork for writing a potentially successful R01 grant application. Moving forward, you will know your deadline to ensure your application arrives at NIH on time, as well as all the steps that must occur in the interim.

The more time and effort you put into your planning process, the more effective it will be and the more smoothly your proposal writing will be. Every grant application requires a great deal of information, work and time, and planning ahead only helps you to stay focus on your goals. ■

Chapter 2: Outlining Your Project and Individual Qualifications

There are specific sections of the National Institutes of Health's (NIH's) R01 grant application that allow you to outline your research topic and direction.

As you approach these areas, think of yourself as a storyteller. You are trying to get the reviewers emotionally involved to the point that they champion your proposal. All good stories have a resolution. Yours will be how your research will advance the scientific field and enable future investigations.

Your story begins with a Project Summary/Abstract, which is a brief yet detailed account of your proposed research. This section is important because initial NIH reviewers will use it to determine the study section that reviews your application. In addition, the Project Summary is the only section of your proposal that every reviewer reads. Most of them will scan the rest of your application, but they all read your Abstract in its entirety.

This chapter tells you what to include and what to leave out of your Project Summary. It also details NIH guidelines pertaining to Abstracts — such as the maximum number of pages — and gives you examples that illustrate what NIH wants to see.

We also examine the Biographical Sketch section, which is more than a simple biography of the principal investigator (PI). There are ways you can creatively use this area to increase your chances of successfully obtaining funding.

The Biographical Sketch section must include a personal statement, an account of the PI's positions and honors, a list of peer-reviewed publications or manuscripts in press, your contributions to science, and research support. This chapter describes each of these elements and how to effectively include them in your Biographical Sketch.

In addition, we explore the requirements for proposals with multiple PIs. You must provide a rationale for using this approach and a description of your plans for making it work. This chapter includes examples of appropriate documentation for applications with multiple PIs.

The chapter also explains how letters of support can help new investigators applying for an R01 grant. It offers suggestions for the type of individual to provide a letter of support, clarifies why you should write the first draft of the letter for these individuals, and includes tips for crafting effective support letters.

FORMULATING YOUR PROJECT SUMMARY/ABSTRACT

Direct from NIH: The NIH Application Guides states:

Project Summary /Abstract

The **Project Summary** is meant to serve as a succinct and accurate description of the proposed work when separated from the application.

State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving the stated goals. This section should be informative to other persons working in the same or related fields and insofar as possible understandable to a scientifically or technically literate reader. Avoid describing past accomplishments and the use of the first person. Finally, please make every effort to be succinct.

This section must be no longer than 30 lines of text, and follow the required font and margin specifications. An abstract which exceeds this allowable length may be flagged as an error by the agency upon submission. This would require a corrective action before the application will be accepted.

As noted above, do not include proprietary, confidential information or trade secrets in the description section. If the application is funded, the Project Description will be entered into an NIH database and made available on the NIH Research Portfolio Online Reporting Tool (RePORT, available at <http://report.nih.gov>) and will become public information.

The attachment must be in PDF format. (See Formatting Attachments for additional information on preparing attachments: <http://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/format-attachments.htm>).

What this means:

NIH states that your Project Summary/Abstract should be “a succinct and accurate description of the proposed work when separated from the application.” Further, “it should be a self-contained description of the project and should contain a statement of objectives and methods to be employed.” It should also outline your application’s broader, long-term goals and specific aims, as well as reference how your proposed research relates to human health, NIH says.

The agency also indicates that your intended audience for this section includes those “working in the same or related fields and insofar as possible should be understandable to a scientifically or technically literate lay reader.” You can expect all of the peer reviewers to read this portion of your grant application.

At the same time, NIH warns that you should not include any proprietary or confidential information or trade secrets in the Project Summary. If your proposal receives funding, the summary becomes part of the public record.

Format Note: The Project Summary can be no longer than 30 lines of text. Effective in 2016, the NIH has begun to provide some flexibility with fonts allowed in PDF attachments. They recommend using the following fonts: Arial, Garamond, Georgia, Helvetica, Palatino Linotype, Times New Roman, and Veranda. The text must be black at 11 point size or larger. You may use a symbol font to insert Greek letters or special characters, but the font size requirement still applies. In addition, there can be no more than 15 characters — including characters *and* spaces — per inch. And there can be no more than six lines of text per inch, using at least half-inch margins on all sides of the 8½” x 11” page.

Keep in mind that initial reviewers in the Center for Scientific Research (CSR) likely will use the Project Summary/Abstract to assign your application to a particular Scientific Review Group (SRG) or study section, as well as to the peer reviewers who will examine it. Therefore, it should contain certain keywords so that SRG staff can readily assign your application and NIH computer systems can retrieve your grant properly. And SRG members who are not primary reviewers probably will rely heavily on your summary to understand your proposal during the group’s general meeting to discuss application fundability.

Many grant-writing experts suggest that you write your Project Summary/Abstract last as you construct your application materials. They maintain that this allows you to gain a more comprehensive understanding of your research proposal.

If you choose to write your Summary/Abstract early, you should consider it provisional and revisit it after you finish writing the rest of your application — especially the research plan — to make sure it is a true reflection of your proposal.

One rationale for writing a provisional Summary/Abstract early is to make sure that your proposal's main ideas are clear and concise in your mind. Once you have written the rest of your application materials, go through them with a highlighter (or the electronic equivalent), and mark all of the key terms that are important to understanding your research. Then revisit your provisional Abstract to make sure every keyword that you highlighted appears in a faithful context.

What to Include

Each of NIH's Institutes, Centers and Offices (ICOs) appears to have a slightly different idea regarding what you should include in this relatively brief description of your proposed research.

For example, the National Cancer Institute (NCI) indicates that your Project Summary should incorporate the following:

- A brief background of the project;
- Specific aims, objectives or hypotheses;
- Significance of the proposed research and relevance to public health;
- Unique features and innovation of the project;
- Methodology (action steps) to be used;
- Expected results; and
- Description of how your results will affect other research areas.

In addition, NCI indicates that the Abstract should succinctly describe every major aspect of the project except the budget. And it should have a distinct section that describes its relevance to public health.

NCI also offers the following suggestions regarding your Project Summary/Abstract:



STRATEGY:

Many grant-writing experts suggest that you write your Project Summary/Abstract last as you construct your application materials.

- Be complete, but brief.
- Use all of the space allowed (30 lines of text).
- Avoid describing past accomplishments and using the first person.
- Write the abstract last so that it reflects the entire proposal.
- Remember that NCI and NIH will use the abstract for purposes other than the review, such as to provide a brief grant description in annual reports, presentations and public dissemination.

The National Institute for Allergy and Infectious Diseases (NIAID), on the other hand, offers different—and quite specific—instructions along with a few similarities:

- In the first sentence, describe the significance of your research to your field and relevance to NIAID’s mission: to better understand, treat, and prevent infectious, immunologic, and allergic diseases.
- Next, state your hypothesis and your research’s innovative potential.
- Describe your Specific Aims and long-term objectives.
- Don’t include graphs or images.

So be sure to examine your potential reviewing institutes’ Project Summary requirements before you finalize this portion of your grant application.

Use Storytelling Tactics to Engage Reviewers

Most reviewers make up their minds regarding your proposal’s merit as they read the first page of your application, according to principal investigators who have served in such roles. And they read the rest of your application looking to support their original impression.

Consequently, the quicker you grab their attention, the more likely you will engage them to support your proposal.

Your Project Summary/Abstract should present the opening chapter of your story, offering a short description of what the reader will find in the narrative. Therefore, the Summary should be a faithful, although condensed, replica of the narrative. NIH reviewers indicate that applicants often submit Abstracts that

contain ideas found nowhere in the application's body, or Summaries that fail to include important ideas that *do* appear in the main sections.

As stated earlier, reviewers use the Project Summary/Abstract to prepare themselves to intelligently read the application as a whole. Therefore, if the Abstract is an unfaithful map, they are like drivers heading into one state while holding a map of another.

A good place to begin your abstract is to get your reviewers' attention by answering four questions:

1. What is the problem or need that your proposal will address?
2. Why is it so important that it must be resolved? In other words, what is the significance?
3. Why are you the only person or group, or best-suited one, who can resolve the problem or need?
4. What is your proposed solution to address the problem?

Look to Project Summary/Abstract Examples

Example 1: NIAID offers the following outstanding example from an actual grant application broken down by the elements NIAID indicates are important for its applications:



REMEMBER:

The Summary should be a faithful, although condensed, replica of the narrative.

Proposal Title: Mechanisms of Integrin-Mediated Costimulation in T Cells	
NIAID- Significant Topics	Abstract
Significance of the proposed research	<p>The integrin 1421 (VLA-4) contributes to the etiology of common autoimmune disorders, including multiple sclerosis, inflammatory bowel disease, and systemic lupus erythematosus. Although VLA-4 is widely viewed as contributing to T cell function by directing cell trafficking and by enhancing cell adhesion, VLA-4 potently costimulates T cell activation.</p> <p>The mechanisms underlying this costimulation are not well understood and may play a significant role in the etiology of human immune disorders.</p> <p>Our long-range goal is to understand how to manipulate the costimulatory functions of VLA-4 in order to regulate T cell activation in vivo. Our immediate objective is to determine how VLA-4 modulates T cell responses to antigen.</p> <p>Here, we present preliminary data characterizing a previously unknown effect of VLA-4 ligation on the movement of signaling complexes induced by the TCR. Our specific hypothesis is that structures containing SLP-76 and ADAP are required for the transmission of tension-dependent costimulatory signals initiated upon VLA-4 ligation.</p>
Innovation and unique features of the proposal	<p>The rationale for the proposed work is that it will provide an enhanced understanding of the fundamental mechanisms that enable the integration of the signaling pathways downstream of the TCR and VLA-4.</p>

Methodology or specific aims	<p>Three aims will examine how ADAP contributes to T cell costimulation and how cytoskeletal tension contributes to VLA-4 dependent costimulatory signals:</p> <ol style="list-style-type: none"> 1. How does ADAP contribute to the assembly and translocation of SLP-76 microclusters? 2. How does costimulation depend on the VLA-4-dependent immobilization of microclusters? 3. How does cytoskeletal tension contribute to T cell costimulation by VLA-4?
Re-emphasis of the proposal's innovation	<p>These studies explore a novel effect of VLA-4 ligation, the lateral immobilization of TCR-induced complexes, and use it as a tool to dissect the pathways involved in costimulation by VLA-4. We expect these studies to define the mechanisms by which VLA-4 ligation costimulates T cell activation.</p> <p>This will have a positive impact on our understanding of autoimmune disease, and will assist in the identification of unique intracellular targets for drug development. This work will also generate insights into the systems linking cell shape to cell growth and proliferation, providing useful insights into cancer.</p>

Example 2: NIAID again breaks down the Abstract by the elements it indicates are important:

Proposal Title: T Cell Epitope Mimicry for Autoimmune Responses in SLE	
NIAID-Significant Topics	Abstract
Significance of the proposed research	Systemic lupus erythematosus (SLE) is a complex, autoimmune disorder predominantly affecting young females. Despite being multigenic, the HLA complex in general and HLA-DR in particular remains the most dominant genetic risk factor for disease susceptibility.
Innovation and unique features of the proposal	<p>A striking feature is the strong association of autoantibody specificities with some HLA haplotypes. This application addresses the mechanisms for this close association.</p> <p>In this application we will test the hypotheses that in lupus patients, molecular mimicry with microbial peptides is responsible for the selective enrichment of T cells reactive with lupus-associated autoantigens.</p> <p>Depending on microbial exposure, the HLA dictates the nature of cross-reactive peptides it binds and thereby the autoantigen selection. This process leads to activation of self-reactive T cells, autoantibody production, epitope spreading and end organ damage.</p>

Methodology or specific aims	<p>Using Ro60 as the candidate autoantigen and HLA-DR and -DQ transgenic mice, following specific aims are proposed to seek evidence for our hypothesis:</p> <ol style="list-style-type: none"> 1. To identify the molecular mimics of T cell epitopes on Ro60. 2. To demonstrate that multiple exposures to peptide mimics of Ro60 T cell epitopes influences the Ro60 reactive T cell repertoire. 3. To determine the pathogenic potential of anti-Ro60 initiated autoimmune responses in lupus-prone NZM2328 mice transgenic for HLA-DR3 and -DQ2. <p>The findings from this application will clearly demonstrate that T cell responses to lupus-associated antigens can initiate autoimmune responses in SLE.</p>
Re-emphasis of the proposal's innovation	<p>This will shift the current paradigm that SLE is predominantly a B cell mediated disease to a more rational model in which both T and B cells have their unique roles in disease manifestation. This will provide a theoretical framework from which rational therapeutic approach can be devised.</p>

Based upon NIAID's examples, we reviewed NCI's Project Summary/Abstract requirements and compared them to actual award-winning grant applications. The following examples are the result of that evaluation.

Example 3: This one correlates NCI’s key elements to the actual Abstract language:

Proposal Title: Molecular Interactions and Restoration Strategies of PTEN and P53 in Gliomas

NCI-Significant Topics	Abstract
Brief background	<p>PTEN and p53 are the most frequently mutated tumor suppressors in human cancer, including gliomas. Recent evidence shows that wild-type PTEN and wild-type p53 (wt-p53) enhance each other’s tumor suppressive functions. Wt-p53 induces PTEN gene transcription and wt-PTEN protects wt-p53 protein from degradation.</p> <p>We recently found, for the first time, that PTEN has unexpected tumor promoting properties in some glioma cells and tumor xenografts. We have preliminary evidence that PTEN acquires these unexpected tumor promoting properties by enhancing the half-life and oncogenic effects of gain-of-function p53 mutants (mut-p53).</p>
Specific aims, objectives, or hypotheses	Based on these findings, we formulate the following novel hypothesis: PTEN tumor suppressor can exhibit tumor promoting properties in the setting of gain-of-function mut-p53.
Significance of the proposed research and relevance to public health	Therefore, therapeutic strategies that aim at restoring PTEN expression or function could lead to varying effects that depend on the mutational status of p53.

Methodology	<p>To test this hypothesis and its prognostic, mechanistic, functional and therapeutic implications, we propose the following studies:</p> <ul style="list-style-type: none">• In aim #1, we will use a large number of banked human glioblastoma specimens to determine the association between the combined PTEN/p53 mutational status and clinical outcome.• In aim #2, we will investigate the mechanism through which PTEN regulates mut-p53 protein levels and function.• In aim #3, we will assess the in vivo effects of restoring PTEN to glioma tumors with varying p53 mutational status.• In aim #4, we will determine if small molecule modulators of p53 can reverse the tumor promoting effects of PTEN in mut-p53 cells and tumors. <p>The results from all aims will be assessed for their consistency with the hypothesis.</p>
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<p>Expected results</p>	<p>Successful completion of the studies proposed in this application would:</p> <ol style="list-style-type: none"> 1. establish the combined PTEN/p53 status as a prognostic parameter (aim 1), 2. uncover previously unknown mechanistic and functional interactions between PTEN and mut-p53 (aim 2), 3. determine conditions and strategies for a successful therapeutic restoration of PTEN (aim 3), and 4. have important clinical implications for the use of small molecule modulators of p53 by identifying a subset of tumors that are more sensitive to these drugs and providing a rationale for their combination with PTEN restoration (aim 4).
<p>How results will affect other research areas</p>	<p>The findings will have important implications on determining patient prognosis and developing new therapies against human cancers.</p>

Example 4: Here, you can see how the Principal Investigator clearly connected the NCI’s key elements to her actual Abstract language:

Proposal Title: HER3 Signaling in Development and Cancer of the Breast

NCI-Significant Topics	Abstract
Brief background	<p>The ErbB family of receptor tyrosine kinases includes EGFR, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4. Abundant evidence supports the causal role of HER2 overexpression in up to 25% of all breast cancers. While HER3 lacks intrinsic kinase activity, HER3 is often overexpressed in breast cancers that overexpress HER2. Heterodimerization of HER2 with HER3 increases proliferation, survival, and transformation of breast cells. Tyrosine-phosphorylated HER3 potently engages the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, which increases tumor cell proliferation and survival. Inhibitors of HER2 such as the monoclonal antibody trastuzumab and the dual EGFR/HER2 tyrosine kinase inhibitor (TKI) lapatinib are currently approved for treatment of HER2-overexpressing metastatic breast cancer. However, many breast cancers with HER2 gene amplification do not respond and/or eventually escape trastuzumab and lapatinib.</p>
Specific aims, objectives, or hypotheses	<p>It is our hypothesis that 1) signaling by HER2:HER3 heterodimers is essential for mammary tumorigenesis, and 2) HER3 expression enhances tumor cell survival, rendering tumors resistant to therapies that target HER2.</p>
Significance of the proposed research and relevance to public health	<p>According to these hypotheses, HER2-positive breast tumors would be less frequent and less malignant in the absence of HER3, and therapeutic antibodies targeting HER3 may prevent or reverse trastuzumab or lapatinib resistance.</p>

<p>Unique features and innovation of the project</p>	<p>These results would support the development of treatments targeting HER3 and its downstream effectors as alternative or adjuvant therapy for patients with HER2-positive breast cancers.</p>
<p>Methodology</p>	<p>We have designed experiments testing this hypothesis, using a novel genetic approach to conditionally eliminate ErbB3 (endogenous mouse HER3) expression specifically in the mammary epithelial cells (MECs) of mice.</p> <ul style="list-style-type: none"> • In Aim 1, we will determine if HER3/ErbB3 is required for development of the mammary epithelium. We will use mice harboring MEC-specific loss of ErbB3 to examine mammary glands at each stage of post-natal mammary gland development. These studies will reveal the role of HER3/ErbB3 in untransformed MECs that may ultimately contribute to transformation. • Experiments in Aim 2 will determine if HER3/ErbB3 is required for mammary tumorigenesis in vivo. We will use genetically engineered mouse models of HER2-driven and HER2-independent breast cancers to determine if ErbB3 is required for their formation and malignant progression. • Aim 3 will determine if HER3 inhibition (genetic and pharmacologically) sensitizes HER2 overexpressing breast cancer cells to anti-HER2 therapies. Mice bearing HER2-overexpressing breast cancers will be treated with monoclonal antibodies targeting HER3 in combination with lapatinib and trastuzumab.
<p>Expected results</p>	<p>In summary, the experiments outlined in this proposal will provide the necessary knowledge with which to determine if selective targeting of ErbB3 might be an alternative choice for advanced therapy tailored to HER2-overexpressing breast cancers, as well as those that do not overexpress HER2.</p>

KEEP YOUR PROJECT NARRATIVE BRIEF

Direct from NIH: The NIH Application Guides states:

Project Narrative

Provide Project Narrative in accordance with the announcement and/or agency-specific instructions. Please click the Add Attachment button to the right of this field to complete this entry.

For NIH and other PHS agencies applications, using no more than two or three sentences, describe the relevance of this research to public health. For example, NIH applicants can describe how, in the short or long term, the research would contribute to fundamental knowledge about the nature and behavior of living systems and/or the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. If the application is funded, this public health relevance statement will be combined with the project summary (above) and will become public information.

A separate Research Plan form is required for NIH and other PHS agencies applications. Refer to Section R.400 - PHS 398 Research Plan Form, Research Plan, for separate file uploads and instructions.

What this means:

Where the Project Summary/Abstract is 30 lines of text targeted toward scientists in the same field, the Project Narrative is much shorter and serves a completely different purpose, NIH maintains.

The agency states the Project Narrative should be no more than two or three sentences describing your proposed research's relevance to the public health arena. In addition, "in this section, be succinct and use plain language that can be understood by a general, lay audience."

The NIH RePORTER online grant award reporting tool often refers to the Project Narrative as the "Public Health Relevance Statement." It appears below — and frequently as part of — the Project Summary/Abstract in the RePORTER tool. As such, the Project Narrative will be part of the public record.

NIAID makes the following suggestions for constructing your Project Narrative:



TIP:

Use lay language in your Project Narrative to describe your project's potential to improve public health in two or three sentences.

- In lay language, describe your project's potential to improve public health in two or three sentences.
- Don't include graphs or other images.

Also, like the Project Summary/Abstract, many grant-writing experts suggest writing the Project Narrative *after* you have completed the bulk of your application. They reason that — at that point — you will have a clearer picture of your proposal's scope and how it impacts public health.

Look at These Examples

With all this in mind, use the following examples of Project Narratives taken from successful NIH grant applications:

Example 1:

Proposal Title: p90RSK: A Flow Responsive Mediator of Inflammation

Project Narrative: The role of inflammation in cardiovascular disease and diabetes has become increasingly evident. At the basic science level understanding the specific signaling events involved in these mechanisms is a key issue that will be addressed here by biochemistry, cell biology, and in vivo transgenic mice. These studies should provide insight into mechanisms by which disturbed flow promotes vascular inflammation and facilitate development of new therapeutic approaches to limit atherosclerosis, especially in DM.

Example 2:

Project Title: Capsid-Targeting HIV-1 Antivirals

Project Narrative: Effective treatment of HIV/AIDS requires the development of novel antiviral compounds that can complement the existing drug arsenal. This research project will define the mechanism of antiviral compounds acting on a novel HIV-1 target — the capsid. The studies proposed herein will facilitate the development of novel therapies and help elucidate the stage of HIV-1 infection termed uncoating.

Example 3:**Project Title:** Signaling Mechanisms in Regulation of Tumor Angiogenesis

Project Narrative: Cancer is currently one of the most prevalent causes of death in the U.S.A., and current therapeutic options aim only to slow the progression of cancer. Therefore, a renewed effort must be made to identify nontoxic endogenous circulating anticancer molecules which could be exploited as therapeutic targets. My laboratory has cloned and expressed one such circulating molecule, and is presently testing it in a cell culture system and in live mice having tumors. The data being developed from these proposed studies have potential applications to cure solid tumor growth (cancers) in which angiogenesis contributes to the disease phase.

USE ALL THE PARTS OF THE BIOGRAPHICAL SKETCH

Direct from NIH: The NIH Application Guides states:

Attach Biographical Sketch: Provide a biographical sketch for each senior/key person. Biographical sketches must follow the format described.

- Include biographical sketches of all senior/key personnel and Other Significant Contributors.
- Use the sample format on the Biographical Sketch Format Page to prepare this section for all (modular and other) grant applications. See: <http://grants.nih.gov/grants/forms/biosketch-blank-format-Forms-D.docx>
- The Biographical Sketch may not exceed five pages per person. This five-page limit includes the table at the top of the first page.
- Complete the education block at the top of the format page beginning with the baccalaureate or other initial professional education, such as nursing. Include postdoctoral training, separately referencing residency and clinical fellowship training, if applicable.

What this means:

NIH limits the Biographical Sketch — also known as the Biosketch — to no more than five pages per person and provides a form for presenting this information. Your application must include a complete Biosketch for all Senior/Key Personnel and Other Significant Contributors.

NIH defines Senior/Key Personnel as the Project Director (PD)/Principal Investigator (PI) “*and other individuals* who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries or compensation are requested under the grant.” Usually, these Senior/Key Personnel have doctoral or other professional degrees, NIH says, adding that you should also include those with master’s and baccalaureate degrees if their involvement meets the above definition.

You will also need a Biosketch for any Other Significant Contributors, those persons who commit to contribute to the project’s scientific development or execution, NIH states. They are usually listed as presenting “effort of zero person months” or “as needed” on your application. Consultants likely will be in this category.



REMEMBER:

The Biosketch is your opportunity to detail your knowledge, skills and ability to perform your proposed research.

The Biosketch is your opportunity to detail your knowledge, skills and ability to perform your proposed research. Demonstrate that you are the individual most qualified to do it. Reviewers scrutinize this section to ensure that you and other investigators and proposed staff have the proper experience with the proposed techniques.

Although NIH limits the Biosketch to five pages per person, the form for this portion is only the first page and provides space only for the key personnel’s education. You then add up to four additional pages to complete the individual’s Biographical Sketch. NIH additionally instructs you to complete this information “beginning with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training, separately referencing residency training when applicable.”

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME:

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE:

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY

Please refer to the Biographical Sketch instructions in the General Application Guide for NIH and Other PHS Agencies, R&R Senior/Key Person Profile Form (See: <http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general/g.100-how-to-use-the-application-instructions.htm>), in order to complete sections A, B, C, and D of the Biographical Sketch.

Samples are also available for your reference here: <http://grants.nih.gov/grants/forms/biosketch-sample-Forms-D.docx>.

What Your Biosketch Should Include

Direct from NIH: The NIH Application Guides states:

Following the educational block, complete sections A, B, C, and D as described below.

A. Personal Statement. Briefly describe why you are well-suited for your role(s) in this project. The relevant factors may include: aspects of your training; your previous experimental work on this specific topic or related topics; your technical expertise; your collaborators or scientific environment; and/or your past performance in this or related fields. Note the following additional instructions:

- For institutional research training, institutional career development, or research education grant applications, faculty who are not senior/key persons are encouraged to complete this section, but not required to do so.
- Applicants for dissertation research awards should include a description of their career goals and intended career trajectory and their interest in the specific areas of research designated in the FOA, in addition to the information outlined above.
- Candidates for Research Supplements to Promote Diversity in Health-Related Research should include a description of their general scientific achievements and/or interests, as well as specific research objectives and career goals, in addition to the information outlined above. Indicate any current source(s) of educational funding.
- If there are factors affecting your past productivity that you wish to explain, such as family care responsibilities, illness, disability, or military service, you may address them in your personal statement.
- Indicate if you have published or created research products under another name.
- You may mention specific contributions to science that are not included in Section C. Do not present or expand on materials that should be described in other sections of this biosketch or the application.
- Figures, tables and graphics are not allowed.

You may cite up to four publications or research products that highlight your experience and qualifications for this project. Research products can include audio or video products; conference proceedings such as meeting abstracts, posters or other presentations; patents; data and research materials; databases; educational aids or curricula; instruments or equipment; models; protocols; and software or netware.

B. Positions and Honors. List in chronological order positions held since the completion of your most recent degree, concluding with your present position. High school students and undergraduates may include any previous positions. For individuals, such as fellowship applicants or career development award candidates, who are not currently located at the applicant organization, include the expected position at the applicant organization, with the expected start date.

List any relevant academic and professional achievements and honors. In particular:

- Students, postdoctorates, and junior faculty should include scholarships, traineeships, fellowships, and development awards, as applicable.
- Clinicians should include information on clinical licensure and specialty board certification, if applicable.
- Include present membership on any Federal Government public advisory committee.

C. Contributions to Science. Candidates for Research Supplements to Promote Diversity in Health-Related Research who are high school students, undergraduates, and postbaccalaureates are not required to complete this section.

Briefly describe up to five of your most significant contributions to science. While all applicants may describe up to five contributions, graduate students and postdoctorates are encouraged to consider highlighting two or three they consider most significant. Descriptions may include a mention of research products under development, such as manuscripts that have not yet been accepted for publication.

Each contribution should be no longer than one half page, including citations. These contributions do not have to be related to this project. For each contribution:

- Indicate the historical background that frames the scientific problem; the central finding(s); the influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology; and your specific role in the described work.

- You may cite up to four papers accepted for publication or research products that are relevant to the contribution.
 - Research products can include audio or video products; conference proceedings such as meeting abstracts, posters or other presentations; patents; data and research materials; databases; educational aids or curricula; instruments or equipment; models; protocols; and software or netware.
 - These citations do not have to be authored by you.

You may provide a URL to a full list of your published work. This URL must be to a Federal Government website (a .gov suffix). NIH recommends using My Bibliography (See: <http://www.ncbi.nlm.nih.gov/books/NBK53595/>). Providing a URL to a list of published work is not required, and reviewers are not required to look at the list.

D. Additional Information: Research Support and/or Scholastic. Note the following instructions for specific types of applicants/candidates:

- High school students are not required to complete this section.
- Applicants for predoctoral and postdoctoral fellowships, dissertation research grants, and candidates for Research Supplements to Promote Diversity in Health-Related Research from the undergraduate through postdoctoral levels should use this section to provide information about their scholastic performance, following the instructions below. In situations where applicants/candidates in these categories also have research support, they should complete both parts of this section.

Research Support

For all other individuals required to complete a biosketch, list selected ongoing and completed research projects for the past three years (Federal or non-Federal support). Briefly indicate the overall goals of the projects and your responsibilities. Do not include number of person months or direct costs.

Do not confuse “Research Support” with “Other Support.” Though they sound similar, these parts of the application are very different.

- As part of the biosketch section of the application, “Research Support” highlights your accomplishments, and those of your colleagues, as scientists. This information will be used by the reviewers in the assessment

of each individual’s qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team.

- In contrast, “Other Support” information is required for all applications that are selected to receive grant awards. NIH staff will request complete and up-to-date “other support” information from you after peer review.

Scholastic Performance

Predoctoral applicants/candidates (including undergraduates and postbaccalaureates): List by institution and year all undergraduate and graduate courses, with grades. In addition, in the space following the chart, explain any grading system if other than 1-100, A, B, C, D, F, or 0- 4.0. Show levels required for a passing grade.

Postdoctoral applicants: List by institution and year all undergraduate courses and graduate scientific and/or professional courses germane to the training sought under this award, with grades. In the space following the chart, explain any grading system if other than 1-100, A, B, C, D, F, or 0-4.0. Show levels required for a passing grade.

What this means:

The Biosketch must include the following sections, but keep in mind that it cannot exceed five pages:

- **Personal Statement** — Here, you should briefly describe why your experience and qualifications make you particularly well-suited for your role (such as Principal Investigator, mentor, etc.). You may also state up to four publications or research products that highlight your experience and accomplishments. This is also the section to explain any gaps in your past productivity.
- **Positions and Honors** — List your previous positions in chronological order, concluding with your present one. Also, list any honors and include any memberships on federal government public advisory committees.
- **Contributions to Science** — Describe up to five of your most significant contributions to science within a half-page or less for each, including citations. For each contribution, reference up to four publications accepted

for publication or research products that are relevant to your stated contribution. You may provide a URL listing all of your published work from a Federal Government website such as My Bibliography.

- **Research Support** — For this section, list both selected ongoing and completed (during the last three years) research projects. Begin with the most relevant to your current proposal, and briefly state the project’s overall goals and the responsibilities of the Senior/Key Personnel. Keep in mind that this is not the place for the number of person months or direct costs.

Now, let’s look at the Biosketch parts one at a time to show how they will affect your application.

Personal Statement

The Personal Statement should detail why you are the best individual for a role in the project.

Reviewers now consider the information you include here when they examine your qualifications. These may include your pedigree, your research experience or your track record of resolving challenges in new areas. You need to point out specifically why you think you are the most qualified person to lead your proposed project.

At the same time, you should avoid sounding as if you are boasting. Instead, reference specific objectives and criteria in your background, grants you have already been awarded and publications that resulted from those grants.

Point to presentations you gave, address changing fields of study, and if you are a new investigator — but not an early-stage one — you can detail your experience working in a national laboratory.

If you have been in the research field for years but never had an NIH grant, the Personal Statement is where you can clearly note that, although you are new to this funding source, you are not an early-stage investigator. That is an important distinction reviewers need to know.

NIH instructs reviewers to be less stringent when judging preliminary data from early-stage investigators because they have not had the resources to perform preliminary research. Reviewers would rather judge you on your track record as a postdoctoral researcher than as a graduate student.



STRATEGY:

In your Personal Statement, reference specific objectives and criteria in your background, grants you have already been awarded and publications that resulted from those grants.

New Investigator Case Study

A Principal Investigator (PI) returns to academia from a successful career as an executive in the biotechnology and pharmaceutical industries, having managed annual budgets up to \$100 million. Prior to that, the PI was in the NIH Intramural Program for 10 years and was awarded NIH tenure decades ago. The PI is also a member of the Institute of Medicine. On the other hand, the PI has never received an NIH grant because funding always came from other sources. In that sense, the PI is a new investigator.

The best way to leverage this PI's unusual background to obtain NIH grant funds is by making it explicitly clear in the Personal Statement. By referencing such items as IOM membership, tenure in a very competitive environment, and responsibility for \$100-million projects, the PI in this example demonstrates her competence, experience and track record to NIH reviewers who are predominantly from academia.

This PI would qualify for the new investigator category, but would not receive any breaks because of “lack of experience.” At the same time, she may be given some leeway in terms of presentation because reviewers would recognize that she was not used to following the NIH format. The PI would be judged as the senior investigator that she is.

EARLY INVESTIGATORS STRESS INDEPENDENCE

Early investigators, obviously, should take a different tack. In particular, they should stress their independence from others at their institutions if they will perform their research in that setting and want the NIH to fund it.

As a result, reviewers suggest that the early investigator's Personal Statement should include such language as the following:

- “Although I did my postdoctoral training here, I have moved on to independent status with my own lab space.”
- “I have been the intellectual behind the project for the last year.”
- “I wrote the grant proposals.”
- “My former mentor is going in a different direction.”



TIP:

Early investigators should stress their independence from others at their institutions if they will perform their research in that setting and want NIH to fund it.

In addition, including a letter from the former mentor would help reinforce that the early investigator is independent and delineate the differences between what he is doing now and what the mentor is continuing to do.

Another key issue for early investigators is the degree of institutional commitment in the form of lab and other work space and position within the organization. The stronger you can indicate your institution's backing for your research proposal, the better your application will fare.

GET CREATIVE

The Personal Statement also offers you the opportunity to clarify who does what — and who pays for what — in a series of experiments involving multiple personnel and funding sources.

Case Study 1: A junior investigator has a K01 grant — for which you, as the Principal Investigator on a renewal R01 grant, are the sole mentor — that has overlapping aims with your renewal R01. The K01 mainly supports salary and not the entire support infrastructure. The R01 has many more aims, but some overlap with the K01. In this case, the question becomes: Should you list the K01 recipient as Senior/Key Personnel or Other Significant Contributor on your R01 if you are not going to use any funding for your proposal as salary for this individual?

For this case, because the K01 is a training or transition grant, you would simply need to explain the relationship between the K01 grant and the parent R01 in your Personal Statement and possibly in the Environment statement because the K01 recipient is a positive feature of the environment. The K01 recipient should complete a Personal Statement for the R01 application as an Other Significant Contributor and use it to explain the relationship between the two grants. You should also explain the salary support issue in the Budget Justification section of the R01 application.

Case Study 2: You have a K award for a small randomized controlled trial on a treatment you developed and will soon submit an R01 application that builds on the data you have collected as part of it. In this case, the questions regarding your Personal Statement become:

- Should you emphasize your status as an early-career and new investigator?
- Should you emphasize how the pilot data were collected as part of the K award?

Here, you should discuss your background, which should clearly reflect your status as both an early-stage and a new investigator. You have already succeeded in the competitive grants environment by receiving a K award and then successfully used that K award to generate experimental results that will lead directly to a larger project of increased scope. Be sure to clearly indicate how your prior work is directly related to and effectively supports the work you propose in the R01. Highlight your ability to think strategically to consider the next question to be answered and how that impacts your proposal.

PERSONAL STATEMENT EXAMPLE

A. Personal Statement

I have the expertise, leadership, training, expertise and motivation necessary to successfully carry out the proposed research project. I have a broad background in psychology, with specific training and expertise in ethnographic and survey research and secondary data analysis on psychological aspects of drug addiction. My research includes neuropsychological changes associated with addiction. As PI or co-Investigator on several university- and NIH-funded grants, I laid the groundwork for the proposed research by developing effective measures of disability, depression, and other psychosocial factors relevant to the aging substance abuser, and by establishing strong ties with community providers that will make it possible to recruit and track participants over time as documented in the following publications. In addition, I successfully administered the projects (e.g. staffing, research protections, budget), collaborated with other researchers,

and produced several peer-reviewed publications from each project. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. The current application builds logically on my prior work. During 2005-2006 my career was disrupted due to family obligations. However, upon returning to the field I immediately resumed my research projects and collaborations and successfully competed for NIH support.

1. Merrylye, R.J. & Hunt, M.C. (2004). Independent living, physical disability and substance abuse among the elderly. *Psychology and Aging*, 23(4), 10-22.
 2. Hunt, M.C., Jensen, J.L. & Crenshaw, W. (2007). Substance abuse and mental health among community-dwelling elderly. *International Journal of Geriatric Psychiatry*, 24(9), 1124-1135.
 3. Hunt, M.C., Wiechelt, S.A. & Merrylye, R. (2008). Predicting the substance-abuse treatment needs of an aging population. *American Journal of Public Health*, 45(2), 236-245. PMID: PMC9162292
- Hunt, M.C., Newlin, D.B. & Fishbein, D. (2009). Brain imaging in methamphetamine abusers across the life-span. *Gerontology*, 46(3), 122-145.

Positions and Honors

This section of the Biographical Sketch is rather straightforward. Here, you should list your employment history — that is, dates, places and the nature of the positions. In addition, include any honors and memberships on any federal public advisory committees.

NIH provides the following example:

B. Positions and Honors

Positions and Employment

1998-2000 Fellow, Division of Intramural Research, National Institute of Drug Abuse, Bethesda, MD

2000-2002	Lecturer, Department of Psychology, Middlebury College, Middlebury, VT
2001-	Consultant, Coastal Psychological Services, San Francisco, CA
2002-2005	Assistant Professor, Department of Psychology, Washington University, St. Louis, MO
2007-	Associate Professor, Department of Psychology, Washington University, St. Louis, MO

Other Experience and Professional Memberships

1995-	Member, American Psychological Association
1998-	Member, Gerontological Society of America 1998- Member, American Geriatrics Society
2000-	Associate Editor, Psychology and Aging
2003-	Board of Advisors, Senior Services of Eastern Missouri
2003-2005	NIH Peer Review Committee: Psychobiology of Aging, ad hoc reviewer
2007-2011	NIH Risk, Adult Addictions Study Section, member

Honors

2003	Outstanding Young Faculty Award, Washington University, St. Louis, MO
2004	Excellence in Teaching, Washington University, St. Louis, MO
2009	Award for Best in Interdisciplinary Ethnography, International Ethnographic Society

Contribution to Science

The Contribution to Science section in the new NIH Biographical Sketch replaces the former section of Selected Peer-Reviewed Publications, and is designed to give you a place to describe up to five of your most significant contributions to science. Each contribution entry has two parts: 1) a description and 2) relevant references of up to four papers accepted for publication or research products. Each contribution should be no longer than one-half page, including citations.

When writing this section, keep the following in mind:

- What do you consider your most **significant contributions** to science? This can be contributions to science in general, to a specific scientific discipline, or a combination.
- The **background** for the scientific question or problem you are highlighting in each contribution
- A **recap of the critical findings** for each
- **How these findings were used** to guide future progress in addressing health-related problems or advancing technology
- What was **your specific role** in the described work?

The NIH provides the following example for Section C.



REMEMBER:

A URL to a full list of your published work is no longer required but NIH recommends using My Bibliography, or another federal website, within Section C.

C. Contribution to Science

1. My early publications directly addressed the fact that substance abuse is often overlooked in older adults. However, because many older adults were raised during an era of increased drug and alcohol use, there are reasons to believe that this will become an increasing issue as the population ages. These publications found that older adults appear in a variety of primary care settings or seek mental health providers to deal with emerging addiction problems. These publications document this emerging problem but guide primary care providers and geriatric mental health providers to recognize symptoms, assess the nature of the problem and apply the necessary interventions. By providing evidence and simple clinical approaches, this body of work has changed the standards of care for addicted older adults and will continue to provide assistance in relevant medical settings well into the future. I served as the primary investigator or co-investigator in all of these studies.

- a. Gryczynski, J., Shaft, B.M., Merryle, R., & Hunt, M.C. (2002). Community based participatory research with late-life addicts. *American Journal of Alcohol and Drug Abuse*, 15(3), 222-238.
 - b. Shaft, B.M., Hunt, M.C., Merryle, R., & Venturi, R. (2003). Policy implications of genetic transmission of alcohol and drug abuse in female nonusers. *International Journal of Drug Policy*, 30(5), 46-58.
 - c. Hunt, M.C., Marks, A.E., Shaft, B.M., Merryle, R., & Jensen, J.L. (2004). Early-life family and community characteristics and late-life substance abuse. *Journal of Applied Gerontology*, 28(2), 26-37.
 - d. Hunt, M.C., Marks, A.E., Venturi, R., Crenshaw, W. & Ratonian, A. (2007). Community-based intervention strategies for reducing alcohol and drug abuse in the elderly. *Addiction*, 104(9), 1436-1606. PMID: PMC9000292
2. In addition to the contributions described above, with a team of collaborators, I directly documented the effectiveness of various intervention models for older substance abusers and demonstrated the importance of social support networks. These studies emphasized contextual factors in the etiology and maintenance of addictive disorders and the disruptive potential of networks in substance abuse treatment. This body of work also discusses the prevalence of alcohol, amphetamine, and opioid abuse in older adults and how networking approaches can be used to mitigate the effects of these disorders.
- a. Hunt, M.C., Merryle, R. & Jensen, J.L. (2005). The effect of social support networks on morbidity among elderly substance abusers. *Journal of the American Geriatrics Society*, 57(4), 15-23.
 - b. Hunt, M.C., Pour, B., Marks, A.E., Merryle, R. & Jensen, J.L. (2005). Aging out of methadone treatment. *American Journal of Alcohol and Drug Abuse*, 15(6), 134-149.
 - c. Merryle, R. & Hunt, M.C. (2007). Randomized clinical trial of cotinine in older nicotine addicts. *Age and Ageing*, 38(2), 9-23. PMID: PMC9002364
3. Methadone maintenance has been used to treat narcotics addicts for many years but I led research that has shown that over the long-term, those in methadone treatment view themselves negatively and they gradually begin to

view treatment as an intrusion into normal life. Elderly narcotics users were shown in carefully constructed ethnographic studies to be especially responsive to tailored social support networks that allow them to eventually reduce their maintenance doses and move into other forms of therapy. These studies also demonstrate the policy and commercial implications associated with these findings.

- a. Hunt, M.C. & Jensen, J.L. (2003). Morbidity among elderly substance abusers. *Journal of the Geriatrics*, 60(4), 45-61.
- b. Hunt, M.C. & Pour, B. (2004). Methadone treatment and personal assessment. *Journal Drug Abuse*, 45(5), 15-26.
- c. Merrylye, R. & Hunt, M.C. (2005). The use of various nicotine delivery systems by older nicotine addicts. *Journal of Ageing*, 54(1), 24-41. PMID: PMC9112304
- d. Hunt, M.C., Jensen, J.L. & Merrylye, R. (2008). *The aging addict: ethnographic profiles of the elderly drug user*. NY, NY: W. W. Norton & Company.

Complete List of Published Work in MyBibliography: <http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/public/1PgT7IEFIAJBtGMRDdWFmjWAO/?sort=date&direction=ascending>

Research Support

In the Biosketch's Research Support section, you should list both ongoing and completed projects, including those with both federal and non-federal funding. Start with the projects most relevant to the current application and briefly indicate their overall goals and responsibilities of the Senior/Key Personnel involved in the current proposal. This, however, is not the place to detail the number of person months or direct costs.

Be sure not to confuse "Research Support" with "Other Support." Although they may sound similar, these parts of the application are quite different. The Biosketch's Research Support section highlights your scientific accomplishments and your role in selected grants. Reviewers will use this information to assess each individual's qualifications for a specific role in the project, as well as their roles on the research team.

The Other Support section, on the other hand, includes information required for all applications that are selected to receive awards. NIH staff will request complete and up-to-date Other Support information from awarded researchers after peer review and then check this information to ensure that the proposed research has not already been federally funded.

NIH provides the following example of the Research Support portion of the Biosketch:

2. Research Support

Ongoing Research Support

R01 DA942367 Hunt (PI) 09/01/08-08/31/16

Health trajectories and behavioral interventions among older substance abusers

The goal of this study is to compare the effects of two substance abuse interventions on health outcomes in an urban population of older opiate addicts.

Role: PI

R01 MH922731 Merryle (PI) 12/15/07-11/30/15

Physical disability, depression and substance abuse in the elderly

The goal of this study is to identify disability and depression trajectories and demographic factors associated with substance abuse in an independently-living elderly population.

Role: Co-Investigator

Faculty Resources Grant, Washington University 08/15/09-08/14/15

Opiate Addiction Database

The goal of this project is to create an integrated database of demographic, social and biomedical information for homeless opiate abusers in two urban Missouri locations, using a number of state and local data sources.

Role: PI

Completed Research Support

R21 AA998075 Hunt (PI) 01/01/11-12/31/13
 Community-based intervention for alcohol abuse
 The goal of this project was to assess a community-based strategy for reducing alcohol abuse among older individuals.
 Role: PI

Letters of Support Can Help New Investigators

Direct from NIH: The NIH Application Guides states:

Attach all appropriate letters of support, including any letters necessary to demonstrate the support of consortium participants and collaborators such as Senior/Key Personnel and Other Significant Contributors included in the grant application. Letters are not required for personnel (such as research assistants) not contributing in a substantive, measurable way to the scientific development or execution of the project. Letters should stipulate expectations for co-authorship, and whether cell lines, samples or other resources promised in the letter are freely available to other investigators in the scientific community or will be provided to the particular investigators only. For consultants, letters should include rate/charge for consulting services and level of effort/number of hours per year anticipated. In addition, letters ensuring access to core facilities and resources should stipulate whether access will be provided as a fee-for-service. Do not place these letters in the Appendix. Consultant biographical sketches should be in the Biographical Sketch section.



REMEMBER:

Letters of support do not fall within the NIH’s application page limit, so you can include as many as you feel are necessary.

What this means:

If you are a young investigator, you can use letters of support from your department chair, collaborator(s) and contractor(s) to fill in any gaps in the capabilities outlined in your Biographical Sketch. The letters can even be from colleagues with whom you have worked. These letters do not fall within the NIH’s application page limit, so you can include as many as you feel are necessary.

For standard R01 applications, NIH reviewers will weigh the importance of letters of support based on whether there is a significant gap in your capabilities that must be filled by a collaborator. In these cases, simply naming a consultant will not be sufficient. You will need a strong, specific letter of support from that individual stating exactly what he will provide to the project and demonstrating enthusiasm for it.

Although technically not required for collaborators who are co-investigators with Biosketches in the proposal, a letter of support may still prove valuable if you have a history of working with the individual.

Also, if you are entering a new field, having a letter of support from an established expert in that field is beneficial. For example, if you have always been a basic bench person but now wish to study a specific disease, getting a clinician with expertise in that disease to write a supporting letter helps to establish your credibility.

The letter should specify what support the person is offering, and it must be plausible. You can write a desired draft for the person to review and sign, but do not make all of your supporting letters look the same. Take the time to determine what aspects of your proposal would be most interesting and relevant to each of your collaborators.

Here are four reasons you should craft the initial draft of your letters of support:

- **Congruence.** You know your grant application strategy best, so your self-written draft letter of support becomes part of that overall strategy. Communicating to others exactly what you need and what to cover — and then asking them to prepare it — can be difficult and time-consuming. If you do it for them, you establish momentum and eliminate any breakdown in communication.
- **Expectations.** Initial conversations with contractors and collaborators when you request letters of support may leave both sides with faulty assumptions regarding what to include. When they see your expectations in the letter you construct for them, however, you avoid potential misunderstandings. This ensures that everyone is “on the same page” from the beginning.
- **Timeliness.** Your grant application is a high priority for you, and you are well aware of any deadlines. But your collaborators and contractors may not have the same priorities, and your letter of support may drop lower on their



TIP:

You can write a desired draft of a letter of support for the person to review and sign, but do not make all of your supporting letters look the same.

to-do list. When you offer to write the letter, you likely will receive a quicker response that meets your deadlines.

- **Facilitation.** Allowing your contractors and collaborators to edit your letters is easier for them than drafting the letters on their own. They can read your letter and offer comments and clarifications without having to start from scratch.

Keys to Crafting Effective Letters of Support

When you write a letter of support, here are a few tips to keep in mind:

- 1. Clarify duties, roles and timelines.** Offer specific details regarding what you expect the collaborator or contractor to do, as well as the deadline. This will avoid potential misunderstandings later. And when individuals other than the applicant write their own letters of support, they are often more vague than what the applicant needs. Therefore, make sure the letter draws attention to what you, as the applicant, have done that is relevant to any NIH requirements — or those of any ICOs that may potentially review it.
- 2. Write it from the contractor or collaborator’s point of view.** Tailor each letter to the collaborator or contractor’s specific duties, and write it as if they wrote the letter. If you prepare more than one letter, make sure to use unique language for each.
- 3. Display enthusiasm.** The letter should convey the individual’s enthusiasm for the project by outlining specifics, such as resource and time commitment and interest in the project’s details.
- 4. Get the standard details correct.** Address the letter according to the grant’s guidelines. It will be going to either the applicant or NIH. Have the final, agreed-upon version written on an institutional letterhead, and have it signed by someone authorized to make the commitment.

In addition, many experts recommend that these letters should have a specific structure, including the following three elements:

- **Statement of support** — Use one to three sentences to show enthusiasm and identify the specific project by name.

- **Supporting paragraphs** — Explain how the individual’s research, expertise and technical skills will support the applicant. Detail the individual’s relevant experience and how it bears on the project, as well as his or her previous track record on similar projects. And if you have worked with them before, describe the project and the results. Finally, explain specific duties to perform, and describe the use of any equipment or other resources.
- **Cordial closing** — The closing’s formality will depend on the relationship between the applicant and the person who is supporting them. If the two have a previous productive working relationship, it can be less formal. If that relationship is more limited, the closing should be more formal.

Multiple PIs Means Additional Documentation

If your proposal includes multiple Project Directors (PDs)/Principal Investigators (PIs), you will have to complete and upload a separate Biographical Sketch for each of the PDs/PIs. In addition, you will have to create and upload a Multiple PD/PI Leadership Plan.

Direct from NIH: The NIH Application Guides states:

For applications designating multiple PD/PIs, a leadership plan must be included. For applications designating multiple PD/PIs, all such individuals must be assigned the PD/PI role on the Senior/Key Profile form, even those at organizations other than the applicant organization. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PD/PIs and other collaborators. Do not submit a leadership plan if you are not submitting a Multiple PD/PI application.

If budget allocation is planned, the distribution of resources to specific parts of the project or the individual PD/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Grant Award.

Attach this information as a PDF file.

What this means:

NIH does not place a page limit on this document, stating only that it should include the following:

- A. The rationale for choosing a multiple PD/PI approach rather than having a single PD/PI to lead the proposed research.
- B. The governance and organization structure of the leadership team and the research project, including:
 - Communication plans;
 - Process for making decisions regarding scientific direction; and
 - Procedures for resolving conflict.
- C. The roles and administrative, technical and scientific responsibilities for the project or program for each of the PDs/PIs and other collaborators.

In addition, if you have planned the budget allocation, your Leadership Plan should detail resource distribution to specific project components or individual PDs/PIs.

NIH offers the following examples of Leadership Plans (http://grants.nih.gov/grants/multi_pi/sample_leadership_plans.pdf), noting that applications should follow any special instructions offered by individual ICOs:

Example 1:

Principal Investigator 1 and Principal Investigator 2 will provide oversight of the entire program and development and implementation of all policies, procedures, and processes. In these roles, PI1 and PI2 will be responsible for the implementation of the Scientific Agenda, the Leadership Plan, and the specific aims, and ensure that systems are in place to guarantee institutional compliance with U.S. laws, Department of Health and Human Services and National Institutes of Health policies including biosafety, human and animal research, data and facilities.

Specifically, PI1 will oversee aim 1 and be responsible for all animal research approvals. PI2 is responsible for aims 2, 3, and 4 including the implementation of all human subjects research and approvals. PI1 will serve as contact PI and will assume fiscal and administrative management including maintaining communication among PIs and key personnel through monthly meetings. He will be responsible for communication with NIH and submission of annual reports. The responsibilities of the contact PI will be rotated to PI2 in even years of the grant award. Publication authorship will be based on the relative scientific contributions of the PIs and key personnel.

Example 2:

Principal Investigator 1 at Institution A will be responsible for the oversight and coordination of project management for aim 1 involving the molecular design and production of vectors expressing tumor-specific antigens. Principal Investigator 2 at Institution B will be responsible for aims 2 and 3 including the in vivo and in vitro testing of vaccines. Each PI will be responsible for his own fiscal and research administration.

The PIs will communicate weekly, either by phone, e-mail, or in person, to discuss experimental design, data analysis, and all administrative responsibilities. All PIs will share their respective research results with other PIs, key personnel, and consultants. They will work together to discuss any changes in the direction of the research projects and the reprogramming of funds, if necessary. A publication policy will be established based on the relative scientific contributions of the PIs and key personnel.

PI1 will serve as contact PI and be responsible for submission of progress reports to NIH and all communication.

Intellectual Property: The Technology Transfer Offices at Institutions A and B will be responsible for preparing and negotiating an agreement for the conduct of the research, including any intellectual property. An Intellectual Property Committee composed of representatives from each institution that is part of the grant award, will be formed to work together to ensure the intellectual property developed by the PIs is protected according to the policies established in the agreement.

Conflict Resolution: If a potential conflict develops, the PIs shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to an arbitration committee consisting of one impartial senior executive from each PI's institution and a third impartial senior executive mutually agreed upon by both PIs. No members of the arbitration committee will be directly involved in the research grant or disagreement.

Change in PI Location: If a PI moves to a new institution, attempts will be made to transfer the relevant portion of the grant to the new institution. In the event that a PI cannot carry out his/her duties, a new PI will be recruited as a replacement at one of the participating institutions.

CONCLUSION

After your Abstract, many reviewers turn to your Biographical Sketch as the next step in their assessment process. They want to make sure you have the skills, background and general acumen to take on the research you are proposing.

And with each of these sections, you have only very limited space to present the details that support your research, education and overall background to demonstrate early in the application that you have a viable proposal worth funding. And you want to grab the reviewers' attention, get them emotionally involved and turn them into champions for your project. ■

Chapter 3: Showing Your Institution's Resources and Commitment

One of the core criteria National Institutes of Health (NIH) reviewers use to score your grant application is the Environment in which you perform the research.

They want to ensure you will have the resources — meaning the institutional support, equipment and physical items — you need to successfully complete your proposed investigation. Additionally, they want to know of any unique features of your scientific environment, subject populations or collaborative arrangements that will benefit your project. You will detail these elements in the Facilities and Other Resources and Equipment sections of the application.

Where you perform your research has not always been so important. In fact, reviewers note that “environment is one of the review criteria that used to be virtually meaningless. Almost nobody got a bad score for it.” As one characterized it, “The only place that a reviewer could find information about [it] was the list of centrifuges and computers, which is really not very helpful.”

Obviously, this is no longer the case.

DETAIL YOUR FACILITIES AND OTHER RESOURCES

Direct from NIH: The NIH Application Guide states:

Facilities & Other Resources

No special form is required but this section must be completed and attached for submissions to NIH and other PHS agencies unless otherwise noted in an FOA. Describe how the scientific environment in which the research will be done contributes to the probability of success (e.g., institutional support, physical resources, and intellectual rapport). In describing the scientific environment in which the work will be done, discuss ways in which the proposed studies will benefit from unique features of the scientific environment or subject populations or will employ useful collaborative arrangements.

For Early Stage Investigators (ESIs), describe institutional investment in the success of the investigator, e.g., resources for classes, travel, training; collegial support such as career enrichment programs, assistance and guidance in the supervision of trainees involved with the ESI's project, and availability of organized peer groups; logistical support such as administrative management and oversight and best practices training; and financial support such as protected time for research with salary support. See http://grants.nih.gov/grants/new_investigators/.

If there are multiple performance sites, describe the resources available at each site.

Describe any special facilities used for working with biohazards or other potentially dangerous substances. Note: Information about select agents must be described in the Research Plan, (Select Agent Research).

What this means:

As you construct the Facilities and Other Resources section, you should answer the following questions:

1. What facilities will you use? Include the following subheadings and describe the capacities (including square footage), pertinent capabilities, relative proximity and extent of availability of each to your project:
 - Laboratory
 - Clinical
 - Animal
 - Computer
 - Office
 - Other, such as machine shop, electronic shop, etc.
2. How will the scientific environment in which you perform your research contribute to your success? Include the following sections, and describe how your studies benefit from unique features of the scientific environment or subject populations and useful collaborative arrangement:
 - Institutional support
 - Physical resources
 - Intellectual rapport
3. For early-stage investigators, describe the following:
 - Institutional investment in your success — for instance, resources for classes, travel and training
 - Collegial support, such as career-enrichment programs, and availability of organized peer groups
 - Logistical support — for example, administrative management and oversight and best-practices training, and financial support such as protected time for research with salary support
4. If there are multiple sites where your research will be performed, describe the resources available at each site.

5. Detail any special facilities you will use for working with biohazards or other potentially dangerous substances. If you are using anything classified as a Select Agent, be sure to describe any special facilities used for working with these substances.

For this section, you should list any distinctive features, which may include the following:

- A unique set of technical capabilities
- Access to a special patient population
- The collaborative nature of interactions between you and your colleagues
- A particular emphasis in a special area, such as neurobiology



TIP:

For early-stage investigators, reviewers look for evidence of how your institution values your research and its level of commitment to helping you succeed.

This not only informs reviewers how your institution supports your research, but also underscores your qualifications as the best person to perform your proposed research. For early-stage investigators in particular, reviewers look for evidence of how your institution values your research and its level of commitment to helping you succeed.

In addition, first-time applicants often find succeeding with a proposal rather challenging. They frequently need assistance with start-up funds, access to graduate students, or departmental support for travel, training, or career-enrichment programs.

And if you are an early-stage investigator still working at the same institution where you performed your postdoctoral work, NIH reviewers may be skeptical of your application — especially if you are nearly in the same research area and your postdoctoral mentor still has active grants. A reviewer likely will wonder if the funds might indirectly benefit the mentor instead of funding you. You must demonstrate that you are independent and that your proposed research is *your* project.

Reviewers may also be skeptical when you are a long-term postdoctoral researcher and your institution offers to make you a research assistant professor — *if* you get a grant. NIH wants to see that your institution has already made you a research assistant professor, not that it is making its commitment to you contingent upon you getting the grant.

Remember that institutional support also addresses your research's feasibility, including your freedom to carry out your research, away from classrooms, advising, committees and other day-to-day duties that compete for your time. Reviewers want to be sure that you will have both time and facilities to tackle the research that you describe.

At the same time, some may believe that NIH chooses reviewers only from “distinguished” institutions, which may create a sense of bias. But the average study section likely offers a geographically and scientifically diverse panel, and many reviewers work at or certainly appreciate the constraints of working at institutions that might lack unlimited resources.

Resources Support Independence

There is no limitation regarding this section's length as long the information you provide specifically relates to your available facilities and resources.

As you write this section, there are some key elements that you should include — if they are applicable to your proposal:

- Support your “intellectual rapport” section by explaining any collaborations with same-institution-based colleagues who impact your proposed research.
- Highlight the unique population of your locality, noting such things as underserved groups, high incidences of specific diseases or conditions, rural/urban setting, etc.
- Stress your access to pertinent resources based upon geography — for example, proximity to veterans' centers, public health facilities, children's hospitals and states' departments of health, among others.
- Underscore proof of institutional support such as mentoring availability, university-based grants, institutional clinical research centers and library support.
- Make sure the Facilities and Other Resources matches your proposal's budget request section.
- Take advantage of the correct adjectives when describing your resources — “specially-constructed modules,” “state-of-the-art laboratory,” “cutting-edge clinical operations,” “dynamic imaging” and “centralized data collection,” to get you started.



REMEMBER:

Institutional support addresses your research's feasibility, including your freedom to carry out your research, away from classrooms, advising, committees and other day-to-day duties that compete for your time.



STRATEGY:

Support your “intellectual rapport” section by explaining any collaborations with same-institution-based colleagues who impact your proposed research.

In addition, if your research will involve animals, you must document the animal facilities in this section. If your institution has accreditation from the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), according to the National Institute of Allergy and Infectious Diseases (NIAID), you do not need to detail basic items such as the number of animal cages. Instead, you only have to note AAALAC accreditation. On the other hand, if your institution does not have this accreditation, then you must spell everything out.

One option as you construct this application document is to use subheads that reflect NIH’s requirements. Although the agency does not require a special form for this document, you might consider the following outline based upon NIH-requested information and suggested items from several university grant administration offices:

Facilities and Other Resources

XXX University/Institution: In this section, outline the general scientific environment in which you will conduct your research and how it will contribute to your proposal’s successful outcomes.

Research Population: If you have human test subjects, include this section and use it to note ways in which your research will benefit from the subject populations in your area.

Research Facilities: Here, indicate how your institution’s resources will support your proposed research. Denote any specific elements that will be available, such as a machine shop, electronic shop, etc., and the extent to which they will be available. Also, mention any additional institution-specific facilities that might impact your proposal — for instance, associated children’s healthcare centers, public clinics, veterans’ hospitals, etc. And if there are multiple research sites, describe the resources available at each.

Biohazard Facility: If your research calls for using biohazards or other possibly dangerous substances, you must describe any special facilities for working with them.

Collaborative Arrangements/Intellectual Rapport: Detail any collaborative relationships with your institutional colleagues — such as mentors and other investigators, among others.

Departmental Resources: In addition to institutional resources, be sure to indicate any within your department or division that may benefit your research.

Institutional Support: As stated earlier, indicating your institution's support for you and your research is key for reviewers, and you should use this section for this purpose. This can include available mentors, administrative support and grant-writing education.

Laboratory: In this section, detail your laboratory space, including the location(s), number of rooms, dimensions and available equipment.

Animal: If your proposal involves using animal test subjects, you should use this section to note AAALAC accreditation or, if that is lacking, provide information regarding animal care resources.

Computer: Here, you should indicate the computers, databases, servers and other data storage/computing equipment available for your project.

Office: Will your institution provide you and your collaborators/staff with office space? If so, you should note this, including location(s), number of office(s) and square footage.

Clinical: Use this section to note clinical facilities that are available at your institution.

If you are an early-stage investigator, you should include all of the above, and you can add the following section for the Facilities and Other Resources document:

Early-Stage Investigator

Resources for Continuing Education: In this section, note any institutional resources for classes and/or training and career enrichment programs.

Institutional Support: You can break this section into the following two areas:

Mentorship: Detail how your institution/department fosters your research efforts through a mentorship program.

Collaboration: If your institution offers organized peer groups, you can note that here.

Logistical Support: Indicate any assistance with administrative management and oversight, as well as training offered regarding best lab management practices and other topics.

Financial Support: If your institution ensures protected time for research with salary support, startup funds or institution-sponsored grants, you should detail that in this section.

Here is an example of a Facilities and Other Resources section from a successful grant application (Tumor Necrosis Superfamily Ligands and Lymphocytes Role in Liver Regeneration, Principal Investigator: Robert A. Anders, MD):

Resources:

Laboratory: Dr. X has 400 square feet of laboratory space located on the 3rd floor of the Cancer Research Building within the 4,000 square foot area encompassing the Division of Gastrointestinal/Liver Pathology laboratory. His laboratory is well equipped for molecular biology work. The laboratory within which Dr. X is situated contains a microfuge (2), vortexers, power supplies, programmable thermal cyclers for PCR, refrigerator/freezers (2 each), a -80 C freezer, environmental shakers, waterbaths (2), fume and biologic safety hoods, gel electrophoresis and preparative balances. In addition, Dr. X has access to 250 square feet of shared facilities on the 3rd floor of the Cancer Research Building, which includes an autoclaving and dishwashing service, a dark room with a film processing unit, cold rooms, a densitometer, and ultra-pure water source, a Stargene Eagle Eye II gel imaging system, a Wallac TriLux multiplate scintillation/luminescence counter, and a cryostat. A dedicated area for cell culture work (~250 square feet) is also located on the 3rd floor immediately adjacent to his research lab in the Cancer Research Building for which space is allocated to Dr. X's lab and contains sterile hood for culture work, incubators (2), water bath, a microscope (1) and a refrigerator/freezer for storing culture related materials.

Shared resources: Within the 4,000 square feet of the Division of Gastrointestinal/Liver Pathology there are many shared resources, which include: an ABI 7300 real-time PCR machine, a NanoDrop spectrophotometer, sequencing

rigs (8), analytic balances, pH meter, a Packard microplate fluorometer, fluorescent microscope with attached computer and image analysis software.

Animal facilities: Dr. X has allocated animal space in the facilities Cancer Research Building. This space consists of up to 250 cages, which is enough to house mice used in this proposal over the 5-year time period. Shared animal facilities are also available in the Broadway Research Building. All animal work related to this proposal by Dr. X's laboratories. All facilities are compliant with local and federal regulations concerning animal work and include procedure rooms, hoods with fume extraction to perform surgeries under anesthesia, euthanizing facilities and storage rooms.

Computers: Dr. X is equipped with two Dell Optiplex GX400 PC computers with Intel Pentium III processor containing CD-ROM/CD-RW, Zip drive, 17" flat screen monitors and networked to a Hewlett-Packard L4050 laser printer. Both computers contain Microsoft Office 2000, Reference Manager version 10, Corel Draw Graphics Suite 11 and GeneCodes Sequencer software as well as Internet access. These computers are also networked to two additional Dell Pentium III computers and a Hewlett-Packard L4500 color laser printer.

The Department of Pathology has provided Dr. X with a Dell Pentium 4 optiplex GX620 computer, which is connected to the university's intranet and the Internet. The computer contains software enabling electronic mailing, Medline literature searches and searches of all major protein and nucleic acid databases. Software programs in the computer include word processing, statistical analysis, spreadsheet analysis, and graphics.

Office: Dr. X's office has 100 square feet of space and is located on the 3rd floor of the Cancer Research Building. His lab space is located a short distance down the hall. Photocopiers, a fax machine and secretarial support are available.

Other: The university's medical institutions have numerous core facilities readily available for use. Dr. X is also a member of the cancer center at the university, which provided access to core facilities at a reduced pricing. These include two DNA sequencing facilities, an oligonucleotide synthesis facility, a laser capture microdissection facility, a cell imaging facility, and the tissue microarray facility. The library is on-campus and most journals are available on line through a campus-wide network. PathPhoto, a full service multimedia facility, is easily accessible.

LIST YOUR AVAILABLE EQUIPMENT

In addition to your institution's resources, your application also must list the equipment available for your research.

Direct from NIH: The NIH Application Guide states:

List major items of equipment already available for this project and, if appropriate identify location and pertinent capabilities.

What this means:

The list includes “major items of equipment.” And be sure to indicate their locations and capabilities. NIH defines “equipment” as “an article of tangible, nonexpendable, personal property that has a useful life of more than one year and an acquisition cost of \$5,000 or more, or the capitalization threshold established by the organization, whichever is less.”

If your institution receives little NIH funding, however, the agency maintains that you should list even basic items.

Here is an example of an Equipment list:

The lab is newly renovated space consisting of four rooms:

One lab is equipped for molecular biology and contains gradient PCR machine in specialized hood, western blotting gel apparatus, digital balances, pH meter, 2 microwaves, and 1 microfuge, refrigerator and 2 water baths. The cyto centrifuge will also be located there.

The second room contains BSL2 space, with 4 biosafety hoods, 5 CO2 incubators, counting microscope and an inverted microscope, 2 tabletop centrifuges, refrigerated and unrefrigerated and 2 waterbaths. The outer area of this room contains a refrigerator and -80 freezer. The variomax from Miltenyi is located here.

The third room contains the analytical Gallos flow cytometer, the Elisa plate reader with computer, 2 centrifuges, and microfuge. In addition, the third room has

a refrigerator for cold supplies, 2 waterbaths, and the fume hood. The TQ prep for blood preparation is located there. There is also a robosep instrument from Stem sep, which we will use to separate the microparticles via magnetic beads.

The fourth room is equipped for an office for the postdocs and has computers with printers and cubicles for each person.

Access to other equipment includes access to milliQ water, ultracentrifuges, Real time PCR machines, Luminex access, access to a dark and cold room.

SHARING PLANS ADDRESS SPECIFIC RESEARCH RESOURCES

NIH wants to know you will appropriately share any resources developed through its grants and requires you to complete three plans as part of your application in certain circumstances:

1. Data Sharing Policy
2. Sharing Model Organisms Policy
3. NIH Genomic Data Sharing (GDS) Policy

Direct from NIH: The NIH Application Guide states:

NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. See Supplemental Instructions Part III, 1.5 Sharing Research Resources.

Note: For proposed studies generating human genomic data under the scope of the GDS Policy, an Institutional Certification may be submitted at the time of application submission, but it is not required at that time; the Institutional Certification however, will be requested as Just-in-Time (JIT) information prior to award. The Institutional Certification, or in some cases, a Provisional Institutional Certification, must be submitted and accepted before the award can be issued.

Attach this information as a PDF file.

1. Data Sharing Policy:

All investigator-initiated applications with direct costs of \$500,000 or greater (exclusive of consortium F&A) in any single year are expected to address data-sharing in their application. Applicants are encouraged to discuss data-sharing plans with their program contact at the time they negotiate an agreement with the Institute/Center (IC) staff to accept assignment of their application as described at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html>.

Applicants are reminded that agreement to accept assignment of applications \$500,000 or greater must be obtained at least six weeks in advance of the anticipated submission date. Instructions related to the data-sharing policy as it is applied to applications and proposals responding to a specific Request for Application (RFA) or Request for Proposals (RFP) will be described in the specific solicitation. In some cases, other Funding Opportunity Announcements (FOAs) may request data-sharing plans for applications that are less than \$500,000 direct costs in any single year.

NIH recognizes that in some cases data-sharing may be complicated or limited by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the HIPAA Privacy Rule. The rights and privacy of individuals who participate in NIH-sponsored research must be protected at all times. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. When data-sharing is limited, applicants should explain such limitations in their data-sharing plans.

For more information on data-sharing, please see: http://grants.nih.gov/grants/policy/data_sharing/ and the NIH Final Policy on Sharing Research Data (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>).

2. Sharing Model Organism Policy:

All applications where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding so that other researchers can benefit from these resources, or state appropriate reasons why such sharing is restricted or not possible. Model organisms include but are not

restricted to mammalian models, such as the mouse and rat; and non-mammalian models, such as budding yeast, social amoebae, round worm, fruit fly, zebra fish, and frog. Research resources to be shared include genetically modified or mutant organisms, sperm, embryos, protocols for genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains.

This expectation is for all applications where the development of model organisms is anticipated, regardless of funding amount.

For additional information on this policy, see the NIH Model Organism for Biomedical Research Web site at: <http://www.nih.gov/science/models/> and NIH Guide Notices OD-04-042: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html>, and OD-04-066: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-066.html>.

3. NIH Genomic Data Sharing (GDS) Policy:

All applications, regardless of the funding amount requested, proposing to generate large-scale human or nonhuman genomic data (e.g., genome-wide association studies (GWAS), single nucleotide polymorphism (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data) are expected to provide a genomic data sharing plan. Investigator and institution responsibilities for data submission and access are governed by the NIH (GDS Policy, NIH Guide NOT-OD-14-124: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html>). Supplemental Information to the Genomic Data Sharing Policy provides examples of genomic research projects that are subject to the policy. Investigators proposing to generate large-scale human genomic data from samples, clinical specimens or cell lines collected after January 25, 2015, are expected to have consent for the use and sharing of genomic and phenotypic data for future research purposes and to be shared broadly, even if the specimens or cell lines are de-identified. Applicants may request exceptions to the NIH consent expectations for compelling scientific reasons in the funding application. For additional information see the GDS website at <https://gds.nih.gov/>.

In addition to the information detailed above, grantees are required to submit an Institutional Certification as part of the Just in Time process (see Part III 1.7 Just-in-Time Policy).

What this means:

These are separate documents that you upload as part of your application, but they do not count toward the application page limit.

Keep in mind that reviewers will comment on your resource sharing plans. If you argue that your resources should not be shared — which is an option in specific situations — they will scrutinize any rationale you propose as well.

Data Sharing Policy

If your grant application requests \$500,000 or more in direct costs in any year of the proposed research, NIH expects you to include a data sharing plan with your proposal. Remember also that if your application is a response to a particular Funding Opportunity Announcement, that announcement might require you to submit this plan regardless of the funding level.

The data sharing plan should consist of a brief, one-paragraph description regarding how you will share your final research data. If the data sharing is limited due to institutional, IRB or other state and Federal laws you must explain such limitations within your plan. Alternatively, if you feel that data sharing is not possible, you should use this plan to explain why.

What to Include

The exact content of your data sharing plan will depend on the data you collect and how you plan to share it. For instance, your data sharing plan might simply describe the following:

- Expected data sharing schedule,
- Final dataset's format,
- Documentation to be provided,
- Whether you will provide any analytic tools,
- If you will require a data sharing agreement, including a brief description of the agreement, and
- Mode of data sharing.



REMEMBER:

If you argue that your resources should not be shared — which is an option in specific situations — reviewers will scrutinize any rationale you propose as well.

Consider the following example from NIH:

This application requests support to collect public-use data from a survey of more than 22,000 Americans over the age of 50 every 2 years. Data products from this study will be made available without cost to researchers and analysts.

User registration is required in order to access or download files. As part of the registration process, users must agree to the conditions of use governing access to the public release data, including restrictions against attempting to identify study participants, destruction of the data after analyses are completed, reporting responsibilities, restrictions on redistribution of the data to third parties, and proper acknowledgement of the data resource. Registered users will receive user support, as well as information related to errors in the data, future releases, workshops, and publication lists. The information provided to users will *not* be used for commercial purposes, and will *not* be redistributed to third parties.

Some data-sharing plans, however, may be more elaborate. For instance, here is an example from an actual grant application from the National Institute of Allergy and Infectious Diseases (NIAID) — Note: Redacted material is indicated by brackets ([]):

Sharing of data generated by this project is an essential part of our proposed activities and will be carried out in several different ways. We would wish to make our results available both to the community of scientists interested in [this disease] and the biology of [its causative agent] to avoid unintentional duplication of research. Conversely, we would welcome collaboration with others who could make use of the vaccine assessment protocols developed in [the project].

Our plan includes the following:

Presentations at national scientific meetings. From the projects, it is expected that approximately four presentations at national meetings would be appropriate. There is an annual [Disease] Study Group meeting, of which the PI is secretary. This one-day meeting of interested persons presents new information on a variety of topics related to [the disease]. It is expected that the investigators from this [project] will be active participants of this focused group.

Annual lectureship. A lectureship has brought to the University distinguished scientists and clinicians whose areas of expertise were relevant to those interested in [the disease]. Lecturers have been [list of names]. Visiting lecturers will be scheduled to interact with the investigators of the project as appropriate with their specific areas of expertise which will provide an opportunity for members to present their work to the visitor.

Newsletter. The [disease interest group] publishes a newsletter which currently has a circulation of [number]. The newsletter's intent is to disseminate new information regarding [the disease]. The activities and discoveries of [the project] will be allocated 20% of the newsletter's coverage.

Web site of the Interest Group. The [interest group] currently maintains a Web site where information [about the disease] is posted. Summaries of the scientific presentation from the [quarterly project] meetings will be posted on this Web site, written primarily for a general audience. [Link to Web site.]

Annual [Disease] Awareness week. Beginning this fall during the week of [date], the [interest group] will be sponsoring a [Disease] Awareness week. As part of that program, there will be a research poster display with discussions. In future years, [the project investigators] will be active participants in this program.

SAGE Library Data. [This project] will generate data from several SAGE libraries. It is our explicit intention that these data will be placed in a readily accessible public database. All efforts will be made to rapidly release data through publication of results as quickly as it is possible to analyze the experiments. Data used in publications will be released in a timely manner. SAGE data will be made accessible through a public site that allows querying as has been set up for a similar project. This site can be accessed at [link to Web site].

Alternatively, if you need to justify why you will not share data or wish to restrict it, NIH offers the following examples:

Example 1

The proposed research will involve a small sample (less than 20 subjects) recruited from clinical facilities in the New York City area with Williams syndrome. This rare craniofacial disorder is associated with distinguishing facial features, as well as mental retardation. Even with the removal of all identifiers, we believe that it would be difficult if not impossible to protect the identities of subjects given the physical characteristics of subjects, the type of clinical data (including imaging) that we will be collecting, and the relatively restricted area from which we are recruiting subjects. Therefore, we are not planning to share the data.

Example 2

The proposed research will include data from approximately 500 subjects being screened for three bacterial sexually transmitted diseases (STDs) at an inner city STD clinic. The final dataset will include self-reported demographic and behavioral data from interviews with the subjects and laboratory data from urine specimens provided. Because the STDs being studied are reportable diseases, we will be collecting identifying information. Even though the final dataset will be stripped of identifiers prior to release for sharing, we believe that there remains the possibility of deductive disclosure of subjects with unusual characteristics. Thus, we will make the data and associated documentation available to users only under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

Example 3

This application requests support to collect public-use data from a survey of more than 22,000 Americans over the age of 50 every 2 years. Data products from this study will be made available without cost to researchers and analysts.

<https://ssl.isr.umich.edu/hrs/>.

User registration is required in order to access or download files. As part of the registration process, users must agree to the conditions of use governing access to the public release data, including restrictions against attempting to identify study participants, destruction of the data after analyses are completed, reporting responsibilities, restrictions on redistribution of the data to third parties, and proper acknowledgement of the data resource. Registered users will receive user support, as well as information related to errors in the data, future releases, workshops, and publication lists. The information provided to users will not be used for commercial purposes, and will not be redistributed to third parties.

Further, if you submit a data-sharing plan, NIH expects you to enact that plan. If you fail to comply — depending on the severity and duration of the noncompliance — the agency can act to protect its interests. For example, NIH may make data sharing an explicit term and condition of any subsequent awards you receive.

The NIH also offers the following as a template example plan for addressing key elements for a data sharing plan under NIH extramural support:

Example Data Sharing Plan for FOA-XX-XXXX**What data that will be shared:**

I will share phenotypic data associated with the collected samples by depositing these data at _____ which is an NIH-funded repository. Genotype data will be shared by depositing these data at _____. Additional data documentation and de-identified data will be deposited for sharing along with phenotypic data, which includes demographics, family history of XXXXXX disease, and diagnosis, consistent with applicable laws and regulations. I will

comply with the NIH GDS Policy and the funding IC's existing policies on sharing data on XXXXXX disease genetics to include secondary analysis of data resulting from a genome wide association study through the repository. Meta-analysis data and associated phenotypic data, along with data content, format, and organization, will be available at _____. Submitted data will confirm with relevant data and terminology standards.

Who will have access to the data:

I agree that data will be deposited and made available through _____ which is an NIH-funded repository, and that these data will be shared with investigators working under an institution with a Federal Wide Assurance (FWA) and could be used for secondary study purposes such as finding genes that contribute to process of XXXXXX. I agree that the names and Institutions of persons either given or denied access to the data, and the bases for such decisions, will be summarized in the annual progress report. Meta-analysis data and associated phenotypic data, along with data content, format, and organization, will be made available to investigators through _____.

Where will the data be available:

I agree to deposit and maintain the phenotypic data, and secondary analysis of data (if any) at _____, which is an NIH-funded repository and that the repository has data access policies and procedures consistent with NIH data sharing policies.

When will the data be shared:

I agree to deposit genetic outcome data into _____ repository as soon as possible but no later than within one year of the completion of the funded project period for the parent award or upon acceptance of the data for publication, or public disclosure of a submitted patent application, whichever is earlier.

How will researchers locate and access the data:

I agree that I will identify where the data will be available and how to access the data in any publications and presentations that I author or co-author about these data, as well as acknowledge the repository and funding source in any publications and presentations. As I will be using _____, which is an NIH-funded repository, this repository has policies and procedures in place that will provide data access to qualified researchers, fully consistent with NIH data sharing policies and applicable laws and regulations.

Sharing Model Organism Policy

If your research anticipates developing model organisms, regardless of your award amount, NIH requires you to include a specific plan for sharing and distributing unique model organisms or indicate why such sharing is not possible or restricted.

Direct from NIH: The NIH Application Guide and Web site (http://grants.nih.gov/grants/policy/model_organism/model_organisms_faqs.htm) state:

All applications where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding so that other researchers can benefit from these resources, or state appropriate reasons why such sharing is restricted or not possible. Model organisms include but are not restricted to mammalian models, such as the mouse and rat; and non-mammalian models, such as budding yeast, social amoebae, round worm, fruit fly, zebra fish, and frog. Research resources to be shared include genetically modified or mutant organisms, sperm, embryos, protocols for genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains.

This expectation is for **all** applications where the development of model organisms is anticipated, regardless of funding amount.

For additional information on this policy, see the NIH Model Organism for Biomedical Research Web site at: <http://www.nih.gov/science/models/> and NIH Guide Notices OD-04-042: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html>, and OD-04-066: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-066.html>.

The term “model organism” includes mammalian models, such as the mouse and rat, and non-mammalian models, such as budding yeast, social amoebae, roundworm, Arabidopsis, fruit fly, zebrafish, and frog. Examples of model organisms for which a sharing plan is expected when new, genetically modified organisms are developed is posted on the NIH Model Organism for Biomedical Research Web site (<http://www.nih.gov/science/models/>). This list is updated periodically. Although genetic variants of viruses, bacteria, and other prokaryotic organisms should be made widely available pursuant to the NIH policy (see FAQ4), at this time NIH is not expecting the submission of a sharing plan from investigators who intend to develop non-eukaryotic organisms. Genetically modified organisms are those in which mutations have been induced by chemicals, irradiation, transposons or transgenesis (e.g., knockouts and injection of DNA into blastocysts), those in which spontaneous mutations have occurred, and congenic or consomic strains. Depending on accepted practice, new, genetically modified model organisms developed with NIH funding may be shared as mature organisms, sperm, eggs, embryos, or even the vectors used to generate transgenic or knockout organisms (refer to FAQ 17). The term “resources” includes materials and data necessary for the production and understanding of model organisms, such as vectors, non-human embryonic stem cells, established cell lines, protocols for genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains.

What it means:

Unlike the data sharing plan, there is no grant award threshold associated with the model organism sharing plan.

Model organisms are new, genetically modified organisms developed for research. Genetically modified organisms are those in which the mutations have been induced by chemicals, irradiation, transposons or transgenesis (for example,

knockouts and injection of DNA into blastocysts), those in which spontaneous mutations have occurred, and congenic or consomic strains. And these new model organisms may be shared as mature organisms, sperm, eggs, embryos or vectors used to generate transgenic or knockout organisms.

Further, model organisms include mammalian models, such as mice and rats, and non-mammalian models, like budding yeast, social amoebae, roundworm, Arabidopsis, fruit fly, zebrafish and frog. You can find examples of model organisms on the NIH Model Organism for Biomedical Research Web site at www.nih.gov/science/models.

The agency also notes that you should make genetic variants of viruses, bacteria and other prokaryotic organisms available under the model organism sharing policy. “At this time NIH is not expecting the submission of a sharing plan from investigators who intend to develop non-eukaryotic organisms.”

When considering the resources that you must share as part of the model organism sharing plan, NIH indicates that you should include “materials and data necessary for the production and understanding of model organisms,” including vectors, non-human embryonic stem cells, established cell lines, protocols for genetic and phenotypic screens, mutagenesis protocols, and genetic and phenotypic data for all mutant strains.

NIH does not place a page limit on your model organism sharing plan and notes that these can range from a simple paragraph to complex, multipage documents.

Here is an example of simple model organism sharing plan from NIH:

As for our plan to share materials and our management of intellectual property, we will adhere to the NIH Grant Policy on Sharing of Unique Research Resources including the Sharing of Biomedical Research Resources Principles and Guidelines for Recipients of NIH Grants and Contracts issued in December, 1999. All model organisms generated by this project will be distributed freely or deposited into a repository/stock center making them available to the broader research community, either before or immediately after publication. Our lab has demonstrated its commitment to sharing by providing ... over the past X years. If we assume responsibility for distributing the newly generated model organisms, we fill requests in a timely fashion. In addition, we will provide relevant protocols

and published genetic and phenotypic data upon request. Material transfers will be made with no more restrictive terms than in the Simple Letter Agreement (SLA) or the Uniform Biological Materials Transfer Agreement (UBMTA) and without reach-through requirements. Should any intellectual property arise which requires a patent, we will ensure that the technology (materials and data) remains widely available to the research community in accordance with the NIH Principles and Guidelines document.

A moderately complicated model organism sharing plan is also possible, and these frequently involve the use of mammalian models. NIH provides this model organism plan example from an application involving mice:

Following the characterization and peer-reviewed publication of the transgenic mouse strain generated, mice will be freely distributed to investigators at academic institutions wanting mice for non-commercial research. Individual requests for shipment of mice generated by this program project funding to AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care International) accredited institutions will be honored. The recipient investigators would provide written assurance and evidence that the animals will be used solely in accord with their local IACAC review; that animals will not be further distributed by the recipient without consent of our Program; that animals will not be used for commercial purposes.

Requests for mice from for-profit corporations to use the mice commercially will be negotiated by our institution's technology transfer office. All licensing shall be subjected to distribution pursuant to my institution's policies and procedures on royalty income. The technology transfer office will report any invention disclosure submitted to them to the appropriate Federal Agency.

In addition, all of the transgenic mice generated will be deposited in at an NIH-supported mouse repository. NIH-supported repositories cryopreserve embryos or sperm and distribute the frozen embryos or mice to biomedical researchers. For the mice I generate I will use standard nomenclature and receive approval from the Mouse Genome Informatic (MGI) nomenclature committee (<http://www.informatics.jax.org/mgihome/nomen/index.shtml>).

To facilitate sharing and distribution of the transgenic/knockout mice and associated resources developed under this grant, mice will be maintained in a specific pathogen-free facility. This facility will maintain the mice free of the following microorganisms and pathogens (e.g., pinworms, mouse hepatitis virus (MHV), Sendai virus, mycoplasma, mites, etc.). Should the transgenic/knockout mice become infected with any of these microorganisms, the mice will be rederived through embryo transfer.

“Other Research Resources” generated with funds from this grant will include DNA constructs, etc. These resources, as available, would also be freely distributed upon request to qualified academic investigators for non-commercial research.

My institution and I will adhere to the NIH Grants Policy on Sharing of Unique Research Resources including the “Sharing of Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts” issued in December, 1999. Specifically, material transfers would be made with no more restrictive terms than in the Simple Letter Agreement or the UBMTA and without reach-through requirements. Should any intellectual property arise which requires a patent, we would ensure that the technology remains widely available to the research community in accordance with the NIH Principles and Guidelines document.

And finally, the model organism sharing plan can become quite complex. Examine the following NIH-offered example:

Special Requirements Section of RFA-XX-OI-011

1. Plans to share research resources. All vectors for transgenic production and mouse strains generated over the past several years have been distributed freely to the broader academic community, either before or immediately on publication. Indeed we have supplied over 250 requested laboratories with either vectors, mice, or both. Requestees typically receive the desired reagents within two weeks to two months of their request, depending on their chronological position in the queue. The infrastructure for this rapid sharing of newly developed reagents (both vectors and mice) continues to be in place in my lab and supported by the Office of Technology and Licensing, Applicant Institution (see attached letter by XXXXX).

2. Intellectual property rights. Consistent with Applicant Institution's policy on intellectual property rights (see attached letter by XXX), my lab will make available any and all strains of transgenic mice produced under this grant for use at other academic or not-for-profit institutions at no cost except for standard maintenance and transportation expenses. (Applicant Institution) will receive the right to use these reagents for educational, research, or other nonbusiness purposes. Applicant Institution may establish a non-exclusive commercial license granting Applicant Institution's rights to use such animals at specific for-profit entities; in these cases, Applicant Institution will maintain the right to grant non-exclusive licenses for use of these materials by academic or not-for-profit institutions.

Transfer of materials to not-for-profit entities will be implemented under terms no more restrictive than the Uniform Biological Materials Transfer Agreement (see example of the Applicant Institution simple letter MTA attached in the appendix). Transfer of materials to for-profit entities will be mediated through the Applicant Institution Office of Technology and Licensing, and typically involves a simple license agreement with execution or annual fees as deemed appropriate, but in no way prohibitive to the ready distribution of these reagents.

Intellectual property rights as pertains to ABC-XYZ reagents. The Non-Profit Institute holds a patent on the use of ABC in mammalian cells. They have made clear that any reagents harboring ABC or XYZ sequences can be freely distributed amongst academic, not-for-profit institutions. Such transfers would be done under a joint Applicant Institution/Non-Profit Institute simple letter MTA (see attached letter from Dr. XXX, Office of Technology and Licensing, Applicant Institution).

Should reagents be transferred to for-profit institutions, an inter-institutional license (Applicant Institution/Non-Profit Institute) will be drafted with execution or annual fees as deemed appropriate, but in no way prohibitive to the ready distribution of these reagents. Those reagents generated in collaboration with Dr. SSSS would require an inter-institutional MTA involving Applicant Institution/Non-Profit Institute/Non-Profit Research Center. These simple agreements are already in place.

Intellectual property rights as pertains to @@@ reagents. For-Profit Company holds a patent on the use of @@@ in @@@@. The memorandum of understanding between For-Profit Company and PHS makes it clear that any and all @@@ containing reagents generated under this grant can be readily shared with the broader academic community under a simple MTA, and do not infringe on the uses under restriction (namely: @@@@, @@@ and @@@). Should our reagents be transferred to for-profit institutions, an inter-institutional license (Applicant Institution/For-Profit Company) will be drafted with execution or annual fees as deemed appropriate. Of course, current For-Profit Company licensing issues as surrounds for-profit institutions would have to be settled between that institution and For-Profit Company.

Intellectual property rights as pertains to the &&& locus. The Non-Profit Research Center holds a license on use of &&& sequences. This license stipulates free use for academic, not-for-profit institutions and involves a simple letter MTA. Those reagents generated in collaboration with Dr. SSSS that incorporate &&& sequences will require an inter-institutional MTA involving Applicant Institution Medical School and Non-Profit Research Center. These simple agreements are currently in place. Should reagents be transferred to for-profit institutions, an inter-institutional license (Applicant Institution Medical School/Non-Profit Research Center) will be drafted with execution or annual fees as deemed appropriate, but in no way prohibitive to the ready distribution of these reagents.

NIH Genomic Data Sharing (GDS) Policy

The NIH decided to extend the Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS), and issued the Genomic Data Sharing (GDS) Policy, effective on January 25, 2015. This policy applies to all NIH-funded research (e.g., grants, contracts, and intramural research) that generates large-scale human or non-human genomic data, regardless of the funding level, as well as the use of these data for subsequent research.

The NIH defines large-scale data to include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data. Sharing of research data supports the NIH mission and is essential to facilitate the translation of research results into knowledge, products, and procedures that improve human health.

Direct from the NIH Web site (https://gds.nih.gov/pdf/NIH_guidance_developing_GDS_plans.pdf):

Elements of a Genomic Data Sharing Plan

For extramural investigators, genomic data sharing plans are to be submitted as part of an application for funding. For all applicants proposing to generate human or non-human data, elements 1 and 2, a description of the data type and the data repository, should be provided at the time of the application. Applicants proposing to generate human data should also provide information addressing elements 3-5 and, if applicable, element 6 prior to award. Applicants proposing to generate non-human data need also to address element 3 prior to award. NIH intramural investigators should submit all relevant elements of the genomic data sharing plan to their NIH Institutes and Center (IC) Scientific Director (SD), or delegate, for review and approval. NIH intramural investigators should have in place an approved data sharing plan prior to start of the research.

- 1. Data Type:** Explain whether the research being considered for funding involves human data, non-human data, or both. Denote the type of genomic data that will be shared (e.g., sequence, transcriptomic, epigenomic, and/or gene expression data) and whether it is individual-level data, aggregate-level data, or both. Also list any other information that is anticipated to be shared such as relevant associated data (e.g., phenotype or exposure data) and information necessary to interpret the data (e.g., study protocols, data collection instruments, survey tools).
- 2. Data Repository:** Identify the data repositories to which the data will be submitted, and for human data, whether the data will be available through unrestricted or controlled-access. For human genomic data, investigators are expected to register all studies in the database of Genotypes and Phenotypes (dbGaP) by the time data cleaning and quality control measures begin in addition to submitting the data to the relevant NIH-designated data repository (e.g., dbGaP, Gene Expression Omnibus (GEO), Sequence Read

Archive (SRA), the Cancer Genomics Hub) after registration. Non-human data may be made available through any widely used data repository, whether NIH funded or not, such as GEO, SRA, Trace Archive, Array Express, Mouse Genome Informatics, WormBase, the Zebrafish Model Organism Database, GenBank, European Nucleotide Archive, or DNA Data Bank of Japan.

- 3. Data Submission and Release Timeline:** Provide a timeline for sharing data in a timely manner. The Supplemental Information to the GDS Policy provides expectations for the timelines of data submission and release based on the level of data processing. In general, NIH will release human genomic data no later than six months after the data have been submitted to NIH-designated data repositories and cleaned, or at the time of acceptance of the first publication, whichever occurs first, without restrictions on publication or other dissemination of research findings. Investigators should make non-human genomic data publicly available no later than the date of initial publication. However, availability before publication may be expected for certain data, projects (e.g., data from projects with broad utility as a resource for the scientific community such as microbial population-based genomic studies), or by the funding NIH IC.

- 4. IRB Assurance of the Genomic Data Sharing Plan:** State whether an Institutional Review Board (IRB) or analogous review body has reviewed the genomic data sharing aspects of your project, or provide a timeline for such review. IRB review of the investigator's proposal for data submission is an element of the Institutional Certification which assures that the proposal for data submission and sharing is appropriate. Please keep in mind that an Institutional Certification is generally required for extramural investigators prior to NIH grant award along with other Justin-Time information or finalization of a contract. For NIH intramural investigators, an Institutional Certification memorandum should be completed and sent from the SD, or delegate, to the IC Genomic Program Administrator (GPA) before research is begun, whenever possible.

- 5. Appropriate Uses of the Data:** The appropriate use of the data should be described. Under the GDS Policy, data is expected to be shared for broad research purposes. If such use of the data is not appropriate, as expressed in informed consent documents of the research participants whose data are included in the dataset, any limitations on the data use should be described in the Institutional Certification. NIH provides standard language to guide the development of data use limitations.

- 6. Request for an Exception to Submission:** If submission of human data generated in the study would not be appropriate because the Institutional Certification criteria cannot be met, the investigator should explain why in the genomic data sharing plan and describe an alternative mechanism for data sharing. If the funding IC grants an exception to submission, the research will be registered in dbGaP and the reason for the exception and the alternative sharing plan will be described. For NIH intramural studies, the NIH Deputy Director for Intramural Research will make the final decision on the exception request, after the IC has made its determination.

What it means:

When writing your GDS plan, you first must state whether you will share the data according to NIH's policy. When making your decision, remember that the GDS Policy applies to all NIH-funded research that generates large-scale human or non-human genomic data and the use of these data for subsequent research.

Include the following details:

- Describe the data to be shared, including the data elements, study populations and study documents. At a minimum, NIH expects you to share data generated and used for funded analyses and documentation sufficient for data interpretation — for example, study protocol and manuals and data collection instruments.

- Detail whether you will include data from all study participants in shared analyses. If you will share only a subset, provide a rationale for this decision, such as tiered consent that addresses sharing.
- Provide a timeline regarding when you will share the data — remember that NIH expects you to share the data once it has been cleaned, or at the time of publication, without restrictions.
- Indicate whether your institutional review board (IRB) or privacy board has approved your application's data-sharing aspects, or the timeline for acquiring such approval. Remember, if your proposal involves human subjects research, NIH typically requires IRB approval prior to awarding a grant or finalizing a contract. IRB assurance of the GDS plan is generally included in the Institutional Certification, and is usually provided along with other Just-in-Time information.
- Outline any use limitations for the shared data. You should determine this by consulting your institution, which will document appropriate uses of the data and limitations as part of the institutional certification. And your institution may request verification of the appropriate data use stated in the data-sharing plan prior to award. For example, your institution may limit use to studies of specific conditions or traits, or certain types of uses or users. Also note any additional consent needed for data sharing in this section.

If you plan not to share data through the NIH GDS data repository, you should include the following information:

- Provide a justification for not sharing. For example, if you are using existing data/specimens, your institution may determine consent is not adequate for data-sharing as described by the NIH GDS policy, and obtaining additional consent may not be possible because of the age of data/specimens, for instance.
- Specify an alternate data-sharing plan if there is a mechanism that is acceptable.

Now, review the following examples of Genomic Data Sharing Plans from NIH:

Example 1: Data from human specimens not yet collected will be shared through NIH-designated data repositories.

Data generated from 800 human samples will be shared through unrestricted-access NIH-designated data repositories; individuals who do not give consent for sharing data will be excluded from the study. Genomic data include individual- and aggregate-level data from whole exome sequencing and genome-wide expression arrays. The study will be registered in dbGaP and the following data and information will be shared through the Sequence Read Archive and Gene Expression Omnibus:

- Study documents (e.g., study protocol, manual of operations, questionnaire, and data abstraction forms)
- Individual-level sequence data produced as part of Specific Aim 1 (i.e., files for single nucleotide polymorphisms)
- Individual-level expression data included in the analyses under Specific Aim 2 (i.e., array data and intensity peaks)
- Associated phenotypic data

The sequence and expression data will be shared once the data have been cleaned and quality control procedures are completed, which is expected to be completed no more than two months after the data have been generated. Data will be generated in years 1 and 2 and submitted in years 2 and 3 of the proposed study. The draft consent form provides consent for the data to be used for future research purposes and to be shared broadly through unrestricted-access databases. The Institutional Certification signed by the Institutional Signing Official will be submitted prior to award, along with any other Just-in-Time information.

The IRB advised that the sequence data produced through this award may be shared through unrestricted-access NIH-designated data repositories, consistent with data sharing under the NIH GDS Policy. The IRB will review the protocol of this project and will assure, prior to funding, that:

- A. The protocol for the collection of genomic and phenotypic data is consistent with 45 CFR Part 46; 10
- B. Data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;
- C. Consideration was given to risks to individual participants and their families associated with data submitted to NIH-designated data repositories and subsequent sharing;
- D. To the extent relevant and possible, consideration was given to risks to groups or populations associated with submitting data to NIH-designated data repositories and subsequent sharing; and
- E. The investigator's plan for de-identifying datasets is consistent with the standards outlined in the GDS Policy.

Example 2: Data are generated from human specimens collected before the effective date of the GDS Policy, and the data will be shared through NIH-designated data repositories.

Genomic data will be generated from specimens that were previously collected from 2,000 study participants. The genotype and relevant phenotype data for participants will be shared through dbGaP, a controlled-access database, once the genotyping data have been cleaned, which we expect to be completed no more than two months after genotyping is finished. Submission of individual-level genome-wide genotype data produced as part of Specific Aim 1 and individual-level phenotypic data related to mood disorders included in the analyses under Specific Aim 2 is anticipated in year 2 of the proposed study.

The consent for the collection of specimens did not directly address the broad sharing of participants' data but did denote their desire to advance science. After careful review, the IRB determined that data submission was not inconsistent with the terms outlined in the consent. The Institutional Certification, which will be provided prior to award along with any other Just-in-Time information, will include the following DUL: "Use of these data is limited to health/medical/biomedical purposes, which does not include the study of population origins or ancestry."

The Institutional Review Board (IRB) advised that the genotyping data generated from 2,000 specimens may be shared through NIH-designated data repositories, consistent with data sharing under the NIH GDS Policy. The IRB has reviewed the study protocol and assures that:

- A. The protocol for the collection of genomic and phenotypic data is consistent with 45 CFR Part 46;10
- B. Data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;
- C. Consideration was given to risks to individual participants and their families associated with data submitted to NIH-designated data repositories and subsequent sharing;
- D. To the extent relevant and possible, consideration was given to risks to groups or populations associated with submitting data to NIH-designated data repositories and subsequent sharing; and
- E. The investigator's plan for de-identifying datasets is consistent with the standards outlined in the GDS Policy.

Example 3: Data are generated from human specimens collected before the effective date of the GDS Policy, and the data cannot be shared through NIH-designated data repositories.

Genomic data from more than 100 genes in the genome will be generated from specimens previously collected from 700 study participants from a small population in Africa. The consent form did not directly address the broad sharing of participants' data nor the risks associated with broad data sharing of these data. Because of the small population and the lack of information in the consent form, the IRB concluded that it is not appropriate to share these individual-level data collected from existing specimens through any NIH-designated repository and is requesting an exception to data deposition be granted. Pursuing a re-consent process for these participants is not a viable option due to the time lapse between acquiring the samples and generating the data. As an alternative data sharing plan, the University has agreed to share aggregate-level data that will be

submitted to dbGaP and to provide a mechanism to facilitate data sharing through direct collaborations with other investigators under appropriate IRB oversight. The aggregate-level data will include aggregated minor allele frequencies and associated p-values. Other investigators may contact the principal investigator if interested in collaborating on a project that requires use of the individual-level data. All future research participants will be asked to sign an amended consent form that is consistent with the expectation of broad data sharing.

Example 4: Data from non-human specimens will be shared through NIH-designated data repositories.

The University will share individual-level genotype data from 1,500 mice by depositing these data in Sequence Read Archive, which is an NIH-funded repository. In addition, the study protocol, manual of operations, and phenotype data will be submitted. The genotype data will be made publicly available no later than the date of initial publication, which we anticipate during year 3 of the proposed research.

CONCLUSION

Environment is one of the core criteria that NIH reviewers will use to assess your grant application. Therefore, you cannot afford to give your Facilities and Other Resources section short shrift. And simply providing a list of lab equipment and supplies that you will have access to will not suffice as well.

You will have to demonstrate that your institution is behind you and your research. And this is particularly true for early-stage investigators.

Similarly, NIH requires you to indicate how you will share your data, model organisms and GDS. This is an effort by the agency to enhance the value of your research and promote additional investigations in your field. The plans you propose for sharing these materials — or refusing to do so — will be part of the materials reviewers will scrutinize and use to assess your application. ■

Chapter 4: Proving Your Research Topic's Significance

Probably the most important parts of your National Institutes of Health (NIH) R01 application are those in which you describe your proposed research. Specifically, these are the Specific Aims and Research Strategy sections. They address your project's Significance, Innovation and Approach, which are three of the five core grant criteria that reviewers use to score your application.

At the same time, these sections will heavily influence your application's Overall Impact score. Unfortunately, there is no template for incorporating overall impact into your application, and there is no section called "Overall Impact" — or even an incentive to simply add a paragraph labeled as such. Instead, the NIH Office of Extramural Research has stated that you should describe "impact" clearly in the words you feel are relevant to your project.

Consequently, we will examine how you can use the Specific Aims and Research Strategy to perform double-duty:

1. Fulfill the Significance, Innovation and Approach criteria
2. Support the Overall Impact of your research

As you address each of these sections, note that NIH limits your Specific Aims to no longer than one page, and the Research Strategy cannot exceed 12 pages for an R01 application.

Language Is Important

Also keep in mind that although terms like "aims," "goals," and "objectives" may seem interchangeable, they have separate meanings within your application.

- **Goals** are strategic and high-level. For instance, "Our goal is to understand signal transduction in breast cancer."
- **Objectives** often are a restatement of your hypothesis in a way that can be falsifiable. For example, if our hypothesis is that the EGF receptor axis is key in mediating steroidal effects on proliferation, your objective would be to determine the mechanism by which that occurs.

- **Aims** are the outlines of your tactics or tasks to be performed. For instance, “Aim 1 is to establish a culture system of primary breast epithelial cells,” or “I have accomplished this aim.”

Or think of it using this analogy:

- Goals are the view from 30,000 feet
- Objectives are the view from 10,000 feet
- Specific Aims are the view from 1,000 feet

SPECIFIC AIMS NAIL DOWN THE STEPS

Direct from NIH:

State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.

List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.

The Specific Aims attachment is required unless otherwise specified in the FOA. Follow the page limits for the Specific Aims in the Table of Page limits at http://grants.nih.gov/grants/forms_page_limits.htm unless specified otherwise in the FOA.

What this means:

In this section, NIH indicates that you should briefly list your research's specific objectives, which may include the following:

- Test your hypothesis
- Solve a specific challenge
- Challenge an existing paradigm or clinical practice
- Address a critical barrier to progress in the field
- Develop new technology.

Individual NIH Institutes, Centers or Offices (ICOs) may have additional suggestions for crafting your Specific Aims. For instance, the National Cancer Institute (NCI) indicates that your Specific Aims should cover the following:

- Broad, long-term goals;
- Specific objectives and hypotheses to be tested;
- Expected outcomes; and
- Impact on the research field.

NCI further recommends that your Specific Aims should include the following sections:

1. Brief narrative to describe the project's long-term goals and the hypothesis(es) to be tested, which you should adequately support with citations and preliminary data. Explain how you will use the results to test the hypothesis.
2. Numbered list of the aims. For clarity, each aim should consist of only one sentence. Use a brief paragraph under each aim if you need to provide detail. Most successful applications have two to four Specific Aims. And be sure that all aims are related — but not necessarily dependent upon each other.
3. Brief statement regarding the overall impact of the research.

Specific Aims are almost always limited to a single page in length, unless otherwise stated in the FOA.

Keep in mind that reviewers usually receive a small, focused project better than a diffuse, multifaceted project.

Some reviewers have called the Specific Aims the most important page in your entire application because it may be the only section unassigned reviewers read to understand your Approach, Innovation and Overall Impact. They may make up their minds immediately whether your work should receive funding, and then read the rest of your proposal searching for details to reinforce their initial opinions.

If they immediately determine that they like your project, they will look for supportive points they can put in their review. On the other hand, if they decide they do not like it, they probably will begin to search for faults.

The Specific Aims is a one-page document that you will upload in the Research Plan Attachments area of the application.

Format Note: The Specific Aims section must follow the general application formatting requirements. You must use one of the following fonts in 11 point size or larger (text in figures, graphs, etc. may use a legible smaller font):

- Arial
- Garamond
- Georgia
- Helvetica
- Palatino Linotype, or
- Times New Roman



TIP:

Keep in mind that reviewers usually receive a small, focused project better than a diffuse, multifaceted project.

You may use a symbol font to insert Greek letters or special characters, but the font size requirement still applies. In addition, there can be no more than 15 characters — including characters *and* spaces — per inch. And there can be no more than six lines of text per inch, using at least half-inch margins on all sides of the 8½” x 11” page.

Overcome Specific Aims Challenges

There are several common challenges that applicants face — and proven ways to overcome them — that specifically apply to their Specific Aims, including the following:

Challenge 1: If your reviewer reads your Specific Aims and finds them interesting but remains unconvinced, she likely will read the rest of your application to determine if your project is feasible. Therefore, be sure to end the page with a brief paragraph that states your work's impact — that is, how your project, if successful, will change your field of research. Spelling this out for the reviewer allows them to easily grasp your proposal's strengths without having to work for it.

For example: “These two innovative methods, as well as the expertise of the team assembled, will combine to examine whether microparticles can offer important windows on the physiologic world of pregnancy and preeclampsia and set the stage for further longitudinal studies that seek to predict preeclampsia to allow for early treatment.”

Challenge 2: Reviewers often make the following comment on the summary statement: “If the first specific aim doesn't work, the whole proposal goes out the window. If the researcher doesn't get a positive result with it, he or she can't do aims 2 or 3, so we're not going to fund this until we see the data that have basically finished Aim 1.”

If the aims follow each other so that Aim 2 follows Aim 1 and Aim 3 follows Aim 2, you must tell the reviewers what you intend to do if you get an unexpected result with Aim 1. Convince them that there is a future to your proposal nonetheless.

The best grant applications are those with interconnected — but not interdependent — aims. Reviewers look for those experiments where the results do not particularly matter because the various outcomes are equally interesting.



STRATEGY:

If the aims follow each other so that Aim 2 follows Aim 1 and Aim 3 follows Aim 2, you must tell the reviewers what you intend to do if you get an unexpected result with Aim 1.

For example, interconnected Specific Aims might include the following:

Specific Aim 1: Test the hypothesis that plasma microparticles detected in pregnant women will reveal physiologic events during gestation and preeclampsia.

Specific Aim 2: Test the hypothesis that proteomics performed on microparticles over gestation and on subsets of microparticles from normal and preeclamptic women will reveal key differences in protein expression patterns associated with preeclampsia.

Challenge 3: If you are submitting a competitive renewal and change the thrust of your research from the original proposal, tell reviewers why you changed the Specific Aims, and detail your new directions. The reviewer will see the summary statement from the initial award and know your original award's Specific Aims.

Some reviewers are very particular about that, wondering, “Did the Principal Investigator succeed in the first five years?” If not, they likely will not give that PI for a second chance. As a result, you must inform reviewers why you changed directions, such as because something came up that was more interesting to pursue or a new technology became available.



TIP:

Three to four aims support enough hypothesis-testing strategies and description within the application and better support the number of researchers under the budget and likely four-year project duration.

Crafting Your Specific Aims

The three or four Specific Aims that make up the body of your research plan are the real engine that drives your application. Why is it usually three or four aims? There is no rule regarding how many aims your proposal should have, but three or four is the average for most NIH R01 applications.

An application with only one or two aims leaves the reviewer to weigh only one or two strategies to test your hypothesis, which means it likely does not have a broad enough scope to truly impact the field.

With more than four aims, space limitations will not allow you to sufficiently describe your aims to convince reviewers you have fully developed them. Three to four aims support enough hypothesis-testing strategies and description within the application and better support the number of researchers under the budget and likely four-year project duration.

You might consider using a standard format for each of your aims using separate sections. One reviewer recommends breaking your aims down into the following:

- **Rationale** — This provides the strategic context, meaning what you are trying to show and why. This is also the place where you defend the specific approach you plan to use, consider alternatives and begin to describe your logic in designing your experiments.
- **Experimental Approach** — Here, detail how the experiments will be performed. Try to build reviewer confidence that you can perform them. For established investigators, you can highlight key papers in your bibliography that support your experience in the proposed techniques. New investigators either must show preliminary data demonstrating such familiarity or recruit collaborators with widely-acknowledged expertise in the method.
- **Outcomes and Alternatives** — Use this section to describe your experiments' potential results and their implications for your proposed model(s).

You should also consider including an experimental flow chart that provides a glimpse into the broader strategic thinking guiding your project. Such flow charts can illustrate how your plan to prioritize between the different approaches, which outcomes confirm — or undermine — your model, and available alternatives if an experiment fails.

Rely on This Example

Here is a Specific Aims example from a successful NIH grant application (Combining Anti-Invasive and Anti-Angiogenic Therapies for the Treatment of GBM, Principal Investigator: Panagiotis Z. Anastadiadis, PhD). Keep in mind that as originally submitted, this section takes up just over one page but here appears on two pages because of our formatting changes:

Instant angiogenesis is a hallmark feature of glioblastoma multiforme (GBM) that contributes to the highly malignant nature of the tumor. Recent studies with the humanized monoclonal antibody bevacizumab, which targets the pro-angiogenic factor VEGF, have demonstrated significant therapeutic benefit in patients with recurrent GBM. Unfortunately, bevacizumab therapy alters the natural history of the disease, and tumor recurrence on anti-angiogenic therapy often is characterized by an aggressive multi-focal disease progression associated with a rapid clinical decline. Thus, with bevacizumab therapy rapidly becoming the standard of care for recurrent GBM, there is an urgent need to understand how anti-angiogenic therapies influence basic tumor biology and to develop novel strategies to overcome the pro-invasive effects of bevacizumab therapy.

Both previous published reports and our preliminary data in an orthotopic xenograft model demonstrate that bevacizumab therapy is associated with increased infiltration of tumor cells at the invading edge and a multi-focal failure pattern. Further, our data suggest that Src family kinase (FFK) activation represents a key factor promoting the migration and invasiveness of GBM cells in culture and in animal models, including bevacizumab-treated animals bearing glioma xenografts. SFKs are crucial mediators of the pro-migratory and transforming function of activated receptor tyrosine kinases, including EGFR, PDGFR and c-Met, which are commonly amplified or activated in human GBM. Consistent with this, dasatinib, a competitive kinase inhibitor that targets all members of the Src family potently suppresses bevacizumab-induced invasion and multi-focal disease. Based on these data, we have initiated a clinical trial within the North Central Cancer Treatment Group (NCCTG) to evaluate the efficacy of combined bevacizumab and dasatinib treatment in the recurrent GBM setting. ***Our overall hypothesis is that inhibition of GBM invasion with dasatinib will significantly increase the efficacy of bevacizumab therapy and suppress invasion and multi-focal disease progression.*** In addition, our preliminary data argue that at least in some cases, resistance to dasatinib treatment *in vivo* correlates with activation of the phosphatidylinositol 3-kinase (PI3K) pathway. Consistent with this, SFK and PI3K inhibitors can act synergistically to suppress the migration of dasatinib-resistant GBM cells, suggesting that dual inhibition of these pathways in patient tumors may further increase therapeutic benefit.

The objectives of this project are to understand the intersection between SFK and VEGF signaling pathways on GBM migration and invasiveness, to define genetic and molecular characteristics that predict responsiveness to combined bevacizumab and dasatinib treatment, and to identify signaling pathways associated with synergy between SFKs and PI3K inhibition when combined with anti-angiogenic therapy. To achieve these objectives we propose the following **specific aims**:

Specific Aim 1. Assess the combined effects of bevacizumab and dasatinib on GBM invasion

Using a panel of human GBM intracranial mouse xenografts we will evaluate the efficacy of dasatinib \pm bevacizumab therapy on overall survival, invasion, and multi-focal pattern of disease progression, and correlate a number of molecular characteristics, including overall expression and activation status of SFKs, activation of critical upstream or downstream SFK effectors, PI3K signaling, as well as the expression of neo-angiogenesis and hypoxia markers with response to treatment. Similar comparisons will also be performed in samples of recurrent GBM patients treated with bevacizumab/dasatinib in the NCCTG clinical trial N0872. Results will be further validated using samples of recurrent GBM patients treated with single agent bevacizumab (Mayo Clinic) or dasatinib (RTOG 0627)

Specific Aim 2. Examine the role of individual SFKs and specific downstream signaling effectors on bevacizumab-induced invasion

Individual GBM lines will be genetically and pharmacologically manipulated to determine the role of individual SFKs on bevacizumab-induced invasion *in vitro* and *in vivo*. The role of specific downstream SFK signaling effectors, including p120ctn, p130cas, Vav2, and Rac1, on bevacizumab-induced invasion will also be tested.

Specific Aim 3. Examine the combined effect of SFK and PI3K inhibition on GBM migration and invasiveness, and test the effects of dual inhibition on bevacizumab responsiveness

We will examine the role of PI3K effectors, including AKT, GSK3b, mTOR and Rac1, on the migration/invasion of GBM cells. We will also determine

synergistic effects of dasatinib with inhibitors of known PI3K effectors, and examine the efficacy of anti-SFK/PI3K/VEGF combination therapy in orthotopic GBM xenografts.

The poor survival of patients with malignant gliomas underscores the need for insights into the mechanisms involved in gliomagenesis and development of resistance to treatment with subsequent identification of targets of therapy and factors responsible for response and resistance. Inhibition of angiogenesis with the monoclonal antibody bevacizumab represents a novel promising direction in glioma treatment. Collectively, the studies in this project are designed to 1) improve our understanding of the role of SFK inhibition with dasatinib in blocking tumor progression on bevacizumab, 2) provide a scientific basis for identifying patients who are most likely to benefit from dasatinib/bevacizumab combination treatment, and 3) test novel combinatorial therapies to more effectively block tumor invasion in bevacizumab treated patients.

RESEARCH STRATEGY HAS 3 PARTS

Direct from NIH:

Organize the Research Strategy in the specified order and using the instructions provided below, or as stated in the Funding Opportunity Announcement. Start each section with the appropriate section heading – Significance, Innovation, Approach. Cite published experimental details in the Research Strategy section and provide the full reference in Section G.220 – R&R Other Project Information Form, Bibliography and Reference Cited section.

Follow the page limits for the Research Strategy in the Table of Page limits at http://grants.nih.gov/grants/forms_page_limits.htm unless specified otherwise in the FOA. Note that the page limit for this attachment will be validated as a single file.

Notice the following new guidelines introduced in Forms D applications:

Updates to application instructions and review language intended to enhance the reproducibility of research findings through increased scientific rigor and transparency. These updates will take effect for most research grant applications (including small business and complex research grant applications) submitted for due dates on or after January 25, 2016. For research contracts, this policy will be effective for proposals received on/after January 25, 2016 and expected to result in contract awards in Fiscal Year 2017 and beyond.

There are four areas of focus for basic principles of rigor and transparency. These areas apply to the full spectrum of research, from basic to clinical:

1. **Scientific premise:** the strengths and weakness of the data and previously performed work upon which the proposal is built upon.
2. **Rigor:** emphasize how the experimental design and methods proposed will achieve robust and unbiased results. A robust approach might include use of appropriate statistical methods, prospective sample size estimation, replicates, or standards (for example, reference reagents or data standards). Robust and credible results are those obtained with methods specifically designed to avoid bias, such as blinding, randomization, and prospectively defined exclusion/inclusion criteria, to name a few.

3. **Relevant biological variables:** If biological variables are known to affect a system or disease model proposed, you need to discuss how you will control for these factors, if necessary. Such variables may include sex, choice of animal model for the study, and underlying health issues for human study subjects.
4. **Authentication of key biological and/or chemical resources:** Research performed with unreliable or misidentified resources can negate years of hard work and eliminate any chance for a study to be reproduced or expanded upon. As such, you need to describe how you will ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

Reviewers will assess whether these four areas have been appropriately addressed by the applicant through revised language defining the peer review criteria.

(1) Significance

- Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.
- Describe the scientific premise for the proposed project, including consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.

(2) Innovation

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.

(3) Approach

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Describe the experimental design and methods proposed and how they will achieve robust and

unbiased results. Unless addressed separately in Item 15 (Resource Sharing Plan) include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.

- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.
- Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans. For example, strong justification from the scientific literature, preliminary data, or other relevant considerations, must be provided for applications proposing to study only one sex.
- If your study(s) involves human subjects, the sections on the Inclusion of Women and Minorities and Inclusion of Children can be used to expand your discussion on inclusion and justify the proposed proportions of individuals (such as males and females) in the sample, but it must also be addressed here in the Approach section.
- Please refer to NOT-OD-15-102 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html>) for further consideration of NIH expectations about sex as a biological variable.
- Point out any procedures, situations, or materials that may be hazardous to personnel and precautions to be exercised. A full discussion on the use of select agents should appear in the Item 5, below.
- If research on Human Embryonic Stem Cells (hESCs) is proposed but an approved cell line from the NIH hESC Registry cannot be identified, provide a strong justification for why an appropriate cell line cannot be chosen from the Registry at this time.

If an applicant has multiple Specific Aims, then the applicant may address Significance, Innovation and Approach for each Specific Aim individually, or may address Significance, Innovation and Approach for all of the Specific Aims collectively.

What this means:

Your 12-page Research Strategy section will have three main parts:

1. Significance
2. Innovation
3. Approach

These correspond to three primary criteria NIH reviewers use to evaluate your proposal, and you should begin each section with the corresponding subheading.

Scientific premise will be reviewed and scored as part of the Significance review criterion. In addition, your Research Strategy will also include a Preliminary Studies section (if it is a new application) or a Progress Report (for renewal and revision applications). You can address these by including the appropriate subheading — Preliminary Studies or Progress Report, depending on the type of application — within one of the main sections listed above.

NIH also allows you to choose to present the Preliminary Studies/Progress Report aim-by-aim or in a section by itself. Keep in mind, however, that veteran reviewers likely will be most comfortable seeing it as a separate section because that is the way they are used to seeing it before the application form changed in January 2010. Consequently, this currently tends to be the more effective strategy.

As you write your proposal, however, you may find that you are describing an aim in the Specific Aims section, and you need to reveal a particular piece of preliminary data to establish your aim's feasibility. You could place the data discussion within the specific aim, or you could include it within a large section of Preliminary Data and reference the specific aim with a statement such as, "As shown before, we have experience using the 454 sequencing system and have been able to do parallel sequencing of all of the RLAs from leukocytes."

Although NIH does not assign page limits for each section, it does suggest that you break up the 12 pages as follows:

- Significance — 10-15 percent (1-2 pages)
- Innovation — 15-20 percent (2-2½ pages)
- Approach — 33-50 percent (4-6 pages)
- Preliminary Data/Progress Report — 25 percent (3 pages)

Keep in mind, however, that these are merely NIH's recommendations. You may find that you need more room for your Approach or Significance, and must take the needed space from another section. For instance, one reviewer recommends presenting a shorter Innovation and using that additional space to better detail your Approach or to show additional data.

Section 1: Significance

Your Research Strategy's Significance should indicate the following, according to NIH:

- The importance of the problem or critical barrier to progress in the field that your project addresses;
- How your proposal will improve scientific knowledge, technical capability and/or clinical practice in one or more broad fields; and
- How your successful project will change the concepts, methods, technologies, treatments, services or preventive interventions that drive this field.

In addition, the National Institute of Allergy and Infectious Diseases (NIAID) suggests that you consider your proposal's significance both in terms of your scientific field's state and your long-term research goals. With this in mind, the institute maintains you should include the following in your Significance section:

- How your research will advance your scientific field.
- What knowledge gaps your proposal will fill, demonstrating that you are aware of these gaps as opportunities.
- The new and unique nature of your work.

- Your successes associated with related grants.
- How your work meets NIH's mission to improve health through science. Reviewers will ultimately judge your application on your research's likelihood to ultimately cure, treat or prevent disease.

Your strategy for this section will also depend upon your audience — meaning your reviewers' expertise in your field — NIAID notes, pointing to two scenarios:

- Scenario 1 — The study section is narrowly focused in your scientific area, allowing you to write less regarding your research's significance.
- Scenario 2 — The study section is more diverse, meaning you must include more significance information.



STRATEGY:

One tactic is to complete your Approach section before tackling the Significance because you will have a clearer overall perspective of your proposal.

Keep in mind also that NIH reviewers use this section to assign your application to an institute for possible funding, and your description obviously will affect that decision.

One other tactic is to complete your Approach section before tackling the Significance because you will have a clearer overall perspective of your proposal.

Further, the National Cancer Institute (NCI) weighs in with these additional tactics for successfully writing this section:

- Carefully review published data in your field, and avoid outdated research. Use citations not only as support for specific statements, but also to establish familiarity with all of the relevant publications and points of view. Someone working in your field may assess your application, and if you do not mention their contributions, they may not favorably review your proposal.
- Highlight your awareness of potential barriers and alternate approaches.
- Point out how others can apply your research to your scientific field and/or related areas.
- Clearly state all public health considerations.
- Demonstrate that you can attain your objectives within your stated timeframe.
- Stress any experimental method innovations, such as new strategies, research methods and/or proposed interventions.

Significance ≠ Impact

Many investigators are unsure regarding the difference between “significance” and “impact.” NIH states that “significance” is how important your research would be if everything worked perfectly, and “impact” is the likelihood that the project, as written, will change the relevant scientific field and make a difference in human health.

In other words, “significance” is whether the project is worth doing, and “impact” is what NIH gets for its money at the end of the project.

At the same time, your research cannot have impact if it is not worth doing, so high scores for both Significance and Impact are important indicators for funding. Nonetheless, if your research plan is seriously flawed or reviewers do not think your team has the necessary experience and resources to complete the proposed experiments, then your proposal likely will not have much impact, even if the topic is highly significant.

How will reviewers be instructed to assess applications to address the NIH policy on rigor and transparency with respect to impact?

According to the NIH:

Reviewers are directed to consider all of the strengths and weaknesses associated with each of the review criteria and weigh them appropriately for the specific application assigned to them. Thus, the NIH policy on rigor and transparency will contribute to the criterion scores and overall impact score of each application, with the exception of Authentication of Key Biological and/or Chemical Resources. Reviewers will be instructed to evaluate scientific premise, scientific rigor, and consideration of relevant biological variables such as sex as part of the significance (scientific premise) and approach (rigor & biological variables) criteria, as well as in their assessment of overall impact. Reviewers will comment on the proposed Key Biological and/or Chemical Resource Authentication Plan as an additional review consideration, but should not consider it in the overall impact score. Details on the updated application instructions, progress reporting, and review language can be found in the following guide notices: Rigor and transparency in research grant applications (NOT-OD-16-011: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html>) Rigor and transparency in career development awards (NOT-OD-16-012: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-012.html>).

For example, if your research involves the connection between obesity and pneumococcal infection, your Significance section might detail how much obesity exists and how much worse the problem of pneumococcal infection is in the obese population. You can then support this statement with statistics to establish the topic's importance in the reader's mind.

Remember, however, that this section should not look like a book report. You should not perform an exhaustive review of related scientific literature. Although you should do a literature review, you do not need to include every paper in your application's Bibliography.

Continuing with the example above, the applicant believes the chronic level of inflammation in obesity changes the way T cells respond to infection, which influences the outcome of a pneumococcal infection. In the resulting Significance section — which should take up one or two pages — the investigator would explain how her proposal would expand the field, is new, etc., based upon NIH guidelines noted above. Therefore, this section might outline how this research could lead to new treatments, vaccines and/or additional research to address pneumococcal infection in the obese population.



REMEMBER:

Your research cannot have impact if it is not worth doing, so high scores for both Significance and Impact are important indicators for funding.

In addition, NIH provides the following details to help clarify the difference between significance and impact:

Significance	Overall Impact
Significance is evaluated and scored independently of the evaluation and scoring of investigators, innovation, approach, and environments	Overall Impact is not a sixth review criterion.
The evaluation of significance assumes that the “aims of the project are achieved” and/or will be “successfully completed.”	Overall Impact is not necessarily the arithmetic mean of the scores for the scored review criteria.
<ul style="list-style-type: none"> Moreover, reviewers should evaluate the significance of the project within the context of a (research) field. For example, autism is a significant field of study, but not all studies (projects) of autism are significant. 	Overall Impact takes into consideration, but is distinct from, the scored review criteria.
<ul style="list-style-type: none"> Research fields may vary widely, so it would be helpful if reviewers identify in their reviews the research fields within which the project addresses an important problem or critical barrier to progress. 	Overall Impact is the synthesis/integration of the five core review criteria that are scored individually and the additional review criteria which are not scored individually.
<ul style="list-style-type: none"> The research field may be focused on a specific area (enzymology) or a specific disease (e.g., autism), or maybe more broadly defined to cut across many health issues (e.g., language training, psychology). 	<p>To evaluate, the reviewers make an assessment of the likelihood for the project to exert a sustained, powerful influence on the research fields involved, in consideration of the scored review criteria and additional review criteria (as applicable for the project proposed).</p> <ul style="list-style-type: none"> Likelihood (i.e., probability) is primarily derived from the investigators’ approach and environment criteria. Sustained, powerful influence is primarily derived from the significance and innovation criteria. Research fields may vary widely, so it would be helpful if reviewers identify in their reviews the research fields they believe will be influenced by each project.

Perhaps one of the biggest influences on your application’s Overall Impact is the Significance section. Therefore, you must tell the reviewer why what you propose is important.

For example, you might begin your Significance section by stating:

“Obesity is associated with increased complications of pneumococcal infection, which is frequently fatal for this population.”

Although this is factually correct, you should go on to explain how much obesity exists and how much worse it is getting. In addition, note how dangerous pneumococcal infection is for the obese population, and include some statistics to support the topic's importance and be very specific.



TIP:

If your research will not affect a large group of people, you can make a translation argument — meaning your results could lead to additional developments.

If your research will not affect a large group of people, you can make a translation argument — meaning your results could lead to additional developments. If your proposal involves basic science, this type of Significance reasoning becomes critical.

Now, let's look at sample Significance language, including where many first-time applicants run into challenges:

“Obesity is a growing problem in the United States, with much of the population overweight or obese. *[Here, you should provide additional specifics so that reviewers have a clearer picture regarding just how many people are affected by this and could potentially benefit from your research.]* And estimates are that the problem will get worse. *[How much worse do you think it will get? Be specific.]* Obesity increases the risk for many problems. *[Like what? Explain that.]* In poignant fact, what kills most obese patients is pneumococcal infection. *[That's a known fact, so you need to tell the reviewer how many.]*”

Constructing Your Significance

When writing your Significance section, you should be able to address all of your main points within roughly four paragraphs using the following plan:

- **Paragraph 1:** Introduce the problem you plan to solve.

Example: “The development of an HIV vaccine that generates broadly-neutralizing antibodies remains an elusive goal. Recombinant subunit glycoprotein vaccines have generated antibody responses that neutralize laboratory-adapted strains or neutralize only very neutralization-sensitive primary isolates of HIV. Recent studies of HIV-infected populations, however, indicate that up to 20 percent of individuals develop significant neutralization breadth. Our laboratory has recently published results indicating that ...”

- **Paragraph 2:** Additional background as needed: Here, cover the most important points that support the first paragraph's information.

Example: “The structure and variability of the HIV envelope protein (Env) creates a significant challenge for generating an effective neutralizing antibody-based vaccine. Env is present on the virion surface as a trimer of heterodimeric gp120(SU)/gp41 (TM) subunits. Gp120 variable loop glycosylation is extensive, creating a barrier to access for antibodies known as the ‘glycan shield’ (REF). The extreme sequence variability of gp120's exposed variable loops creates the need for either targeting highly conserved regions.”

- **Paragraph 3:** Hit significance hard by describing the approach that will overcome any difficult challenges.

Example: “In this application we describe an approach that will overcome the difficult challenges described above. Using a polyvalent immunogen with a novel combination of molecular adjuvants, we hypothesize that a broad neutralizing antibody response against HIV primary isolates will be generated. Indeed, preliminary data presented later in this application are strongly supportive that this approach will be successful. Experiments described in this application will extend these findings to the SIV/macaca model, providing sufficient proof-of-principle to support the development of this regimen for human studies.”

- **Paragraph 4:** Emphasize the significance in a broader context.

Example: “Results from this study will be significant not only in advancing the development of new generations of vaccines for HIV, but also will provide fundamental new knowledge regarding the nature of B cell signaling pathways and the adjuvants required to optimize affinity maturation in a vaccine context. Broad-based neutralizing responses may be of great benefit against a number of pathogenic viruses, including ...”

In addition, be sure to use plain language to mention the following:

1. Why the results stemming from your hypothesis and plan are important.
2. How your findings will change science or medicine.
3. If lives will be saved or if the quality of life will be improved and how.
4. What new rationales for treatment you will test and why.

Essentially, tell the reviewer what you are going to achieve that's different.

Learn From This Example

You can refer to the following Significance example from a successful R01 application (Capsid-Targeting HIV-1 Antivirals, Principal Investigator: Christopher R. Aiken, PhD) as you're writing your own:

Significance

Formerly a veritable death sentence, HIV infection has become a manageable disease that requires lifelong therapy. Various combinations of small molecule drugs targeting the viral reverse transcriptase (RT) and protease (PR) enzymes are tailored to inhibit replication to low or undetectable levels while minimizing the emergence of drug-resistant viral mutants. These drugs are highly effective, yet are expensive, exhibit significant side effects, and can engender viral resistance via acquisition of mutations. Thus there is a need for continued development of compounds directed against novel viral and cellular targets. By blocking multiple viral functions essential for replication, the effectiveness of antiretroviral therapy can be improved, with the ultimate hope that elimination of the virus from an infected individual can someday be achieved.

HIV enters cells by fusion of viral with cellular membranes, releasing the viral core into the cytoplasm of the target cell. The biochemistry of the fusion reaction is relatively well understood, yet the ensuing early post-entry steps in infection are obscure. The HIV-1 core consists of the genomic RNA and associated proteins (NC, IN, RT) encased by the conical viral capsid. The capsid is a polymer of the CA protein arranged in a lattice of hexameric units (8, 26). The CA protein consists of two domains connected by a flexible linker. The N-terminal domain (NTD) interacts to form the hexameric ring, while the C-terminal domain (CTD) makes dimeric contacts between the CA hexamers (26). The viral capsid is metastable; intact cores containing a complete viral capsid can be purified at 4°C, and these cores shed the CA protein spontaneously when incubated at 37°C. Disassembly of the viral capsid in the target cell has recently emerged as a key step in infection, a conclusion that is based on several lines of evidence. First, our group has shown that mutations in the viral capsid protein (CA) that alter the stability of the viral capsid also lead to reduced infection, owing to an impairment in reverse transcription in the target cell (16). Second, cells express restrictive proteins that potently block retrovirus infection at an early post-entry stage by targeting the capsid (3, 35, 40), likely perturbing virus uncoating in target cells (41). The host protein cyclophilin A (CypA) also play an essential role in HIV-1 infection by associating with the viral capsid (5, 18, 44). The CypA-CA interaction can be disrupted by treatment with cyclosporine A (CsA) or mutations in CA, leading to impaired infection of target cells (21, 37). Third, we describe herein a novel small molecule that inhibits HIV-1 infection by binding to CA and destabilizing the viral capsid. Collectively these studies indicate that HIV-1 infection is sensitive to changes in capsid stability and that the viral capsid is an attractive target for therapeutic intervention.

There are currently no clinically approved therapies targeting the HIV-1 CA protein, but two molecules targeting HIV-1 CA have been reported. CAP-1 is a small molecule that binds to CA near the base of the N-terminal domain and inhibits HIV-1 assembly *in vitro* (23, 42). CAP-1 has weak antiviral activity in replication assays, and studies of resistance have not been performed, perhaps because of weak potency of the inhibitor. Such studies are critical for understanding the mechanism of action and specificity of antiviral compounds. A second CA-targeting molecule, CA-I, is a peptide that was identified via phage-display technology (39). CA-I binds to HIV-1 CA and inhibits CA assembly in

vitro (43). Recently, a “stapled,” i.e., conformationally constrained, version of CA-I was reported to inhibit HIV-1 infection (57). Antiviral peptides are useful for proof-of-principle studies and have been used clinically, though there are significant problems associated with production and delivery of such inhibitors. Therefore, small molecule inhibitors are generally preferable to peptides as therapies.

Compounds targeting viral capsids have been utilized extensively to study the process of picornaviral uncoating. Specifically, compounds in the WIN series of inhibitors, discovered at Sterling-Winthrop in the 80's, bind to a cleft in the poliovirus capsid and inhibit uncoating (11, 17, 56). Structural analysis of WIN compound binding to virions has shown that only minor conformational changes in the capsid are induced, suggesting that the compounds act by “locking down” the capsid, thus preventing conformational changes required for capsid disassembly (20). By selecting for poliovirus resistance to WIN 51711 in culture, two types of resistance mutations were identified in each the four capsid proteins: one class inhibited compound binding, and did not result in drug dependence, while mutations of the other class did not abolish binding of the inhibitor but destabilized the viral capsid (30). The latter mutations also render PV infection dependent on the inhibitor (29). Thus, mutations in the viral capsid can lead to WIN compound resistance by altering capsid stability, which reduces the fitness of the virus in the absence of the inhibitor. Although the WIN compounds were not fully developed for clinical use, the compounds proved very useful as probes for picornaviral capsid function.

In collaboration with Dr. X at [the company], we have recently initiated studies to understand the mechanism of novel inhibitors that were identified by [the company's] drug discovery efforts. Several small tripeptide-like compounds were found to inhibit HIV-1 replication by targeting the viral CA protein. The compounds had no effect on RT or PR activity in vitro, and analysis of viral mutants that were selected for resistance to one of the compounds revealed that resistance is conferred by changes in CA. [The company] has no plans to pursue development of these inhibitors, but has provided them to us for to pursue basic studies of HIV-1 capsid function. In this R01 application, we propose a comprehensive set of studies involving virology and structural biology to further define the mechanism of action of this class of compounds. In addition to defining a novel antiviral mechanism and potentially facilitating the development of new antivirals, these studies will result in an improved understanding of HIV-1 capsid function, thus elucidating the process of HIV-1 uncoating.

Section 2: Innovation

You should use the Innovation section of your Research Strategy to explain the following, according to NIH:

- How your proposal challenges and seeks to alter current research and clinical practice standards.
- Any new theoretical concepts, approaches or methodologies; instrumentation or interventions you plan to develop or use; and how these are better than existing methodologies, instrumentation or interventions.
- Refinements, improvements or new applications of theoretical concepts, approaches or methodologies, instrumentation or interventions.

In addition, NIAID advises applicants to be careful with this section.

Demonstrating how your work is new and unique and how it will add significantly to what is known is sufficient evidence of innovation, the institute states in its online Research Plan Tutorial and Flowchart. If your proposal involves highly innovative approaches, on the other hand, you must build a strong case to challenge current models and your reasons for doing so.

At the same time, NCI recommends that your Innovation section should be no longer than a page and include the following:

- Why your proposal's concepts and methodology are new to your research field.
- How your study design and outcomes are new.
- Any novel findings from preliminary data you will detail in the Approach section.

Therefore, to show your project's pioneering nature, you should present it in the context of what is already known regarding your field and what the challenges are. You can accomplish this with a brief, concise background section. And then you can clearly state what is new and groundbreaking about your proposal.

Do not make the reviewer guess where the novelty is, and do not be afraid to use the word "innovative." For example, consider the following:

"This work is innovative because it will characterize the microparticles in plasma of pregnant women in a rigorous way that will lead to new methods to diagnose abnormal pregnancies."

And although NIH presents three bullet points in its directions for the Innovation section, you do not need to make each a subhead and address them individually in your application, reviewers say. The bullet points are good guidelines, and if you cover them all, you can be confident that you have a thorough Innovation section. But do not organize your information by bullets or subheads. Rather, provide a narrative that demonstrates you have thought about the pioneering nature of what you are proposing and that you have considered how your approach is different from others. In fact, some reviewers recommend that your Innovation section should be no longer than a paragraph or two.

Be aware that some reviewers will focus their attention on the techniques you use — to the virtual exclusion of other considerations. There is still a way to emphasize the innovative components of your application if your work is based upon applying established techniques in a groundbreaking way to solve an important challenge. Namely, describe the endpoint of your experiments, if they work as planned, and then explain what is new and novel about the information you will have at the end of your project.

If you have been truly novel in applying established techniques, you will have a unique set of data that addresses a previously unanswered question — and therein lies your innovation.

At the same time, your proposal must be feasible, which means being too creative can present challenges for reviewers because they are established investigators. They have an eye for what they feel will not work, which makes them somewhat skeptical if your research is too creative, some reviewers say.

There are essentially two ways to address this:

1. Data — The data you present in your Preliminary Data section can convince reviewers. As part of that section, you should not only present the data, but also explain what you feel it means.
2. Track record — Your personal history as a research scientist is also vitally important to show that you know what you are doing regarding a highly innovative approach within your research. Your published works, employment history, education — essentially anything that allows you to demonstrate that you can think outside the proverbial box.



STRATEGY:

Describe the endpoint of your experiments, if they work as planned, and then explain what is new and novel about the information you will have at the end of your project.

How your reviewers respond to your Innovation section typically involves how deeply they have read in their own research fields, how broadly their knowledge extends into other fields, and how much novelty and risk they are willing to tolerate. Historically, however, reviewers are mostly conservative and often do not support work at the earlier, potentially more pioneering stages. Consequently, if your proposal involves decidedly groundbreaking work, you might consider an R21 grant instead of an R01 so you can establish preliminary data (if it is currently unavailable) before moving forward with an R01.

Review This Example

Here are a few examples of Innovation sections:

From Plasma Microparticles Reveal Physiology of Normal and Preeclamptic Pregnancies (Principal Investigator: Dorothy E. Lewis, PhD):

Innovation

These studies are high risk, high reward, in that characterization of microparticles over gestation and in preeclampsia has not been done. The hypothesis that they are indicative of physiologic events in vivo is novel and testable. We have considerable expertise in flow cytometric methods and a long-term interest in maternal health. These attributes make us the ideal group to perform these studies. Coupled with the subset proteomics approaches, we will greatly advance understanding of the physiology of pregnancy and the development of biomarkers for preeclampsia.

From Engineering fibrin polymers for enhanced angiogenesis (Principal Investigator: Thomas Harrison Barker, PhD):

In this project, we first propose to engineer “designer” peptides based on fibrin knob sequences that enable exquisite control over both the association (k_a) and dissociation (k_d) of the peptide to fibrin’s polymerization pockets. Then, utilizing these engineered sequences, we will demonstrate the capacity to alter the biochemical features of fibrin polymer systems by generating a recombinant “plug-and-play” expression system that will enable the production and delivery

of engineered integrin-specific fibronectin domains (as well as other potentially therapeutic proteins) into fibrin polymer systems. Additionally, utilizing various polyethylene glycol (PEG) configurations (e.g., monofunctional, bifunctional, and multifunction-branching) coupled with our engineered synthetic fibrin knob variants; we will demonstrate the ability to alter the polymer network ranging from complete inhibition of polymerization (in the case of mPEG) to the potential blend of fibrous and amorphous polymer (bPEG & mbPEG). Finally, the “designer” fibrin will be optimized for endothelial cell invasion and angiogenesis using specifically designed microfluidic chambers for *in vitro* angiogenesis assays and *in vivo* models of angiogenesis, i.e., the chick chorioallantoic membrane (CAM) model and subcutaneous wound chamber assays.

Section 3: Approach

The Approach section is the heart of your Research Strategy. This is where you will provide the details of your research to convince reviewers that you understand what the work entails and have the resources and expertise to conduct the research.

According to NIH, you should use this section to detail the following:

- Your overall strategy, methodology and analyses you plan to use to accomplish your specific aims. And if you have not included a separate resource-sharing plan, you should use this section to indicate how you will collect, analyze and interpret data, as well as any resource-sharing plans as appropriate.
- Scientific rigor and relevant biological variables
- Potential challenges, alternative strategies and benchmarks for success that you anticipate to achieve your aims.
- If your project is in the early development stages, note any strategies to establish feasibility and how you plan to manage any high-risk aspects.
- Any hazardous procedures, situations or materials and precautions you will use to address them.

NIAID further recommends that you follow these strategies for this section:

- Describe the first set of experiments for each Specific Aim.
- Define the potential next steps for the aims, but do not describe them in detail. This may lend itself to a flowchart or decision tree where you can indicate that if you get result X, then you will follow plan X, but if you get result Y, you will follow plan Y.
- Provide enough experimental detail to demonstrate to reviewers that you understand what your proposal involves and can effectively conduct the research.
 - If you are a more experienced investigator, cite relevant work to show your expertise.
 - If you are a new investigator, indicate you can handle an experimental method, and particularly point out if you have used it before. If you have, cite it, and skip the description.
 - If you lack the expertise to accomplish the work, point out colleagues who do. Their Biosketches should highlight experience that supports their roles on your application.
 - Outline your methods in less detail than you would in a publication. Provide more detail for unique or new methods, and keep graphics simple because they are clearer and can save space.
- Explain experiments to which you bring a unique ability.
 - If your first experiments are ordinary or contracted out, focus instead on those that you bring something unique to and that are interesting.
 - Next, describe your strategy, showing subsequent experiments based upon the results.
 - Draw connections between your personal statement and other Biosketch information, highlighting what you are doing that's different and what you do well.
- Incorporate milestones and timelines, assessing whether they are appropriate as you write.
- If you do not need the information to support your case, leave it out of the Approach section. Reviewers will look for flaws and heavily penalize you for them. So do not give them ammunition by including anything you feel you do not need.

- Include a timetable showing how and when you will accomplish your Specific Aims, noting any overlap of experiments and alternative paths. NCI also suggests that your Approach include the following additional details:
 - For early-stage projects, your strategy to establish feasibility and address high-risk aspect management
 - New methodologies used and why you feel they are an improvement.

Further, NCI notes that you should number your Approach sections to correspond to your Specific Aims numbers. And you may include the preliminary data or progress report before the Specific Aims or integrate the data/report as part of your methods description for each aim.

The Institute also recommends that you avoid excessive experimental detail by referring to publications that describe your methods. Keep in mind that any publications you cite should be your own if possible. And indicate why you will use one approach or method (if applicable) — and include the “how” *and* the “why” — rather than others because this will demonstrate that you simply did not overlook any alternatives. If you are using a complex technology for the first time, be sure to demonstrate your familiarity with the experimental details and potential challenges. If necessary, add a co-investigator or consultant who is familiar with the technology.

If your application involves proposed collaborations and offers of materials or reagents that have restricted availability, document this with letters from the individuals involved, NCI says.

Finally, note that if you propose to use human embryonic stem cells (hESCs) and wish to use a cell line that is not an approved cell line from the NIH hESC Registry, you must “provide a strong justification for why an appropriate cell line cannot be chosen at the time of application” in the Approach section.

Allow Enough Time

Because the Approach is so central to your Research Strategy section, you will spend most of your proposal-writing time on it. And it is what reviewers will spend most of their time evaluating. They will be especially careful to scrutinize it for potential problems, alternative strategies and benchmarks for success.



REMEMBER:

Reviewers will be especially careful to scrutinize the Approach for potential problems, alternative strategies and benchmarks for success.

NIH's Office of Extramural Research last year looked at the five key criteria — Approach, Significance, Innovation, Investigators and Environment — and how well scores for each correlated statistically with an applicant's Overall Impact score. Based upon this analysis, the Approach score turned out to be the best predictor of the final impact score, with a correlation coefficient of 0.82.

The Approach section is also where many new Principal Investigators make one or more of the standard errors that are relatively easy to identify and describe. If this is the case, your Summary Statement may include such stock critiques as the following:

- The applicant is overly ambitious
- Scientific rigor was not adequately addressed
- One or more aims are unfocused or underdeveloped
- An aim is just a fishing expedition for a missing gene or interactions
- There is too little description of results analysis
- The applicant over-relies on a preferred hypothesis
- An aim is just too risky.

Reviewers may genuinely identify these flaws in a grant application, but they occasionally invoke them as a cover when they lack enthusiasm for a proposal and cannot precisely articulate why. Anticipating these critiques during your proposal writing is one of the best defenses you have, and knowing that the Approach score provides the strongest correlation to your Overall Impact score shows that this section is where you should devote most of grant preparation time.

Keep in mind that reviewers do not want to see details like which restriction enzymes you are going to use and which buffer goes with particular restriction enzymes or the brand of mass spectrometer you are going to use. What they are really interested in is your thought process regarding how you will accomplish each aim, including the following:

- Have you carefully thought through the problem you are trying to solve?
- What is your initial plan of attack?
- How likely is that plan of attack to work?
- Did you include a succinct description of the experimental design and methods with enough detail to assure the reviewers that the necessary



TIP:

Anticipating critiques during your proposal writing is one of the best defenses you have, and knowing that the Approach score provides the strongest correlation to your Overall Impact score shows that this section is where you should devote most of grant preparation time.

elements of rigor will be addressed?

- What are the possible things that could go wrong?
- What aspects of feasibility have you not yet demonstrated?
- What is your plan for dealing with those problems if the experiments do not work?

To address the stock critiques above, some reviewers suggest that you spend a paragraph or two explaining the rationale of each aim, noting why you are doing it and outlining the experiment related to each one. You should also choose figures, tables or other visual data that allow reviewers to understand that you are the expert, careful and will do what you say you will.

You will also want to tie the different areas of your application together to better support your proposal. For instance, if you are demonstrating the feasibility of recruiting a target sample size in a psychosocial treatment outcome study, you will want to discuss your ability to recruit a specific number of participants in both the Environment/Resources section *and* in your Approach. The ability to recruit adequate patient population is that crucial to clinical studies. In this case, you would use one sentence in the Approach to document annual patient accruals and/or past successes in recruiting patients, and then use the Environment section to provide slightly more detail regarding why your institution is such a good place to do the clinical research with access to your target study population.

In addition, for research that involves nonstandard, nontrivial “data analysis” needs, be sure to sufficiently describe those needs in your Approach because this will inspire reviewer confidence in your project. With the Research Plan’s 12-page limit, you should use approximately a half-page for this, or as much as a full page if your data analysis is particularly complex and integral to your success. If your project is a biomarker study or clinical trial, for example, remember that NIH will assign statisticians to specifically evaluate the statistical design and power issues, which you must discuss in your Approach.

You can also use your Approach section to provide details regarding novel aspects of your work. For instance, you plan to use a better, more innovative

method of calculating sample size that reviewers likely will not recognize. Should you stick with the more conventional sample-size calculations? Or put the more sophisticated method in an appendix?

Neither. Instead, you should reference a publication that explains the new method and provide a brief description of its advantages in your Approach. If you feel you need a larger explicative discussion, seek your review officer's permission to submit it as supplemental material once you have your study section assignment.

Example Proves Helpful

Since successful applications using Form D are not yet available, below are examples taken directly from a slide deck prepared by Jennifer Kemp, instructor and medical writer for the Department of Medicine at the University of Colorado, to illustrate a suggested way to address the new requirement of describing scientific rigor (e.g.: statistics), biological variables (e.g.: sex).

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].

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.

Example 3

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.

Preliminary Data for New Applicants

Direct from NIH:

Preliminary Studies for New Applications: For new applications, include information on Preliminary Studies. Discuss the PD/PI's preliminary studies, data, and or experience pertinent to this application. Except for Exploratory/Developmental Grants (R21/R33), Small Research Grants (R03), and Academic Research Enhancement Award (AREA) Grants (R15), preliminary data can be an essential part of a research grant application and help to establish the likelihood of success of the proposed project. Early Stage Investigators should include preliminary data.

What this means:

NIH introduced this section in January 2010 as part of its application overhaul, and you should include this only if your application is new. And keep in mind that this section is included as part of your 12-page Research Strategy.

Although reviewers will not place as much emphasis on Preliminary Data for early-stage investigators as they do for more established researchers, every new R01 application should include details regarding the project director(s)/principal investigator(s)'s preliminary studies, data and/or experience related to the proposal.

In addition, NIAID indicates that this preliminary data shows that you are on the right track with your research, and your Specific Aims should build on this previous research as a foundation. "Reviewers use this section together with the biographical sketches to assess the investigator peer review criterion, reflecting your competence to do this work," the Institute states. Therefore, preliminary data builds reviewer confidence that you can handle the technologies involved, understand the methods and effectively interpret the research's results.

NIAID suggests that you include the following details in your Preliminary Studies section:

- Critically interpret preliminary results.
 - Provide alternative meanings to the data to show you have thoroughly considered the problem and can meet future challenges.
 - If you are not critical of your own results, you can be sure reviewers will be.
- Include sufficient information to show you know what you are talking about.
 - The more complex your proposal, the more data you will need.
 - Explain how your early work has prepared you for this new project.
- Focus on *your* preliminary or unpublished data from your lab, although you may include other people's publications. If you present results from other labs, be sure to clearly indicate which data are yours and which are not.
- Include previous experience that shows you can direct the proposed research and achieve its aims.

What to Include and What to Leave Out

The first purpose when presenting preliminary data is to demonstrate feasibility and that you have the necessary expertise to carry out the procedures you propose in the Research Methods. Consequently, some applicants wonder if they should include contradictory data in their applications.

In response, reviewers point out that this section's purpose focuses more on your ability to successfully collect and analyze the data rather than on the results of that data.

Preliminary data supporting your hypothesis and research plan, however, are potent evidence in your favor. They indicate that you are on the right track, and reviewers weigh this heavily. At the same time, there are subtleties to reporting this data, and possible variations involve the following:

1. Primacy of the outcomes,
2. Positive/negative results, and
3. Statistical power of your preliminary studies to detect effects.

And there are several possible outcomes and resulting implications for your proposal based upon your preliminary data:

Positive/ Null/ Negative Results	Statistical Power	Implications
Positive	Adequate	Reviewer may wonder why you need to conduct the proposed study because you already have strong support for your hypothesis
Null/Negative	Adequate	This result presents the biggest potential challenge for your proposal because your preliminary data shows you failed to detect effects, although you had adequate power to do so.
Positive	Inadequate	This is your most desirable potential outcome. Because the statistical power was insufficient to detect effects, your statistical test for this outcome presumably was not significant (if it is, you have to suspect chance). Therefore, you are on the right track with your preliminary studies, and your results bear the replication you are proposing.
Null/Negative	Inadequate	Although this situation presents a challenge, you can address it by implying there was inadequate statistical power to differentiate between the means as not to be believed or is a product of chance.

Courtesy: William Gerin, PhD

Your main challenge with preliminary data is the null result as your primary outcome. This is not necessarily fatal if your sample size was small and your statistical power was inadequate. In this case, you would not necessarily have to mention the data's statistical power, and the reviewer will examine the sample size and understand the limitations there.

When you do present contradictory data, be sure to then explain what you have done to generate confirmatory data that supports your hypothesis.

Review This Example

Here is a partial example of a Preliminary Studies section from a successful NIH application (Combining Anti-Invasive and Anti-Angiogenic Therapies for the Treatment of GBM, Principal Investigator: Panagiotis Z. Anastasiadis, PhD):

Preliminary Data

C1. Serially transplantable xenograft model of human glioma. A number of different animal models of human GBM have been created to date. Conventional GBM cell lines grown in culture fail to maintain proper EGFR and PTEN signaling, often losing both EGFR amplification and wild type PTEN function. As a result, orthotopic xenograft models of these cell lines fail to accurately represent key features of GBM biology and do not invade surrounding brain tissues. Induced overexpression of oncogenes, i.e., mutant EGFR or v-src, in glioma cell lines also fail to accurately recapitulate GBM biology since any oncogene changes in these tumors are clonal, instead of heterogeneous at the cellular level (as is the case in the majority of GBMs) and the degree of oncogene overexpression/activation is super-physiological. A panel of GBM xenograft lines that are established and maintained by direct tumor implantation into the flank of nude mice is propagated in the laboratory of our collaborator. Orthotopically transplanted tumors from these cell lines preserve the histopathologic characteristics of the derivative primary human specimens, and importantly, display a similar invasive potential to the original tumor [83]. Over 20 GBM xenograft lines have been generated to date, and eight of them, representing a wide spectrum of genetic variability associated with human GBM, including EGFR/PDGFR amplification, inactivation of PTEN, expression of mutant EGFRvIII, deletion of p16, and p53 mutation will be used in these studies. *Based on the preservation of both the genetic and histopathologic characteristics of human GBM, we believe that this serially transplantable xenograft model system provides a unique test-bed for the evaluation of novel therapeutic strategies directed against GBM.*

C2. SFK activity in untreated GBM xenografts is associated with invasion. SFKs modulate key signaling pathways implicated in driving tumor invasion in GBM. As a preliminary test of whether SFKs might influence invasion in our xenograft model, we evaluated the expression and activation levels of Src and the downstream effector p120 catenin in a panel of our xenograft lines by western

blotting and compared these levels to the extent of tumor invasion based on an evaluation of H&E tumor sections. As seen in Figure 2, there was a spectrum of Src activation across the xenograft lines evaluated. Interestingly, the three tumor lines (GBM6, GBM8, and GBM26) with the highest level of Y228 phosphorylation of p120-catenin are the most invasive tumor lines. Of specific interest, GBM10 has modest levels of active Src, but low levels of Y228 p120 phosphorylation, and untreated GBM10 tumors exhibit limited tumor invasiveness. These data are consistent with previous studies suggesting that SFKs play a central role in mediating glioma tumor invasion [43, 72-75, 79].

SFK-mediated signaling through the p120-catenin/Vav2 and the p130/DOCK180 pathways modulates Rho family GTPases, which supervise reorganization of the cytoskeleton to permit cell migration. To evaluate whether these signaling pathways were active in GBM, we used immunohistochemistry in orthotopic GBM xenografts to evaluate the activation status of these SFK-dependent pathways within the non-invasive tumor core and at the invading tumor edge. Consistent with the role of SFKs in driving tumor invasion, SFK activation is dramatically higher at the leading/invading edges of xenografted GBM tumors. Likewise, SFK-mediated phosphorylation of a number of direct SFK substrates, including p120, p130cas and Vav2, was specifically observed at the invasive tumor edge but not in the tumor core. SFKs directly affect the cytoskeleton, while p120 and p130cas-dependent pathways critically modulate Rho GTPases; consistent with activation of these pathways, Rho GTPase-dependent phosphorylation (at Ser3) of the actin severing enzyme cofilin [84] is also upregulated at the invasive tumor fronts (data not shown). Moreover, consistent with these pathways being modulated by SFKs, treatment of mice with dasatinib significantly suppressed SFK phosphorylation and downstream signaling events (not shown) in mice with orthotopic GBM tumors. Furthermore, treatment of SF767 glioma cells with dasatinib suppressed the phosphorylation of SFKs at Y416, p120 at Y228, p120cas at Y410, and inhibited Rac1 activity in pull-down assays (data not shown). Collectively, the data argue that increased SFK activity is associated with an invasive phenotype in GBM xenografts and that dasatinib can block both SFK activation and downstream signaling events in animal models of human GBM ...

Progress Report for Renewal/Revision Applications

Direct from NIH:

Progress Report for Renewal and Revision Applications. For renewal/revision applications, provide a Progress Report. Provide the beginning and ending dates for the period covered since the last competitive review. Summarize the specific aims of the previous project period and the importance of the findings, and emphasize the progress made toward their achievement. Explain any significant changes to the specific aims and any new directions including changes to the specific aims and any new directions including changes resulting from significant budget reductions. For any studies meeting the NIH definition for clinical research, discuss previous participant enrollment (e.g., recruitment, retention, inclusion of women, minorities, children etc.) as part of the progress report, particularly if relevant to studies proposed in the renewal or revision application. You should not submit a PHS Inclusion Enrollment Report form unless the enrollment is part of new or ongoing studies in the renewal or revision application.

A list of publications, patents, and other printed materials should be included in the Progress Report Publication List attachment; do not include that information here.

Attach this information as a PDF file.

If you are submitting a renewal or revision application, you will provide a progress report rather than preliminary studies information. This progress report should contain the following information:

- Your project period beginning and end dates.
- A summary of your findings' importance as related to your Specific Aims.
- Changes to specific aims, if any
- Test subject accrual, if your study is a clinical trial
- Published and unpublished results, highlighting your progress toward achieving your Specific Aims.

When writing these reports, reviewers recommend that you indicate the dates and restate the Specific Aims. Then you should include a narrative summary of the progress you have made for each aim. At the same time, you will not have to relist your publications because you will upload them as a separate document. Ideally, your progress report should be no more than two pages.

OVERALL IMPACT BRINGS EVERYTHING TOGETHER

Direct from NIH: https://grants.nih.gov/grants/peer/guidelines_general/impact_significance.pdf

Significance: Does the project address an important problem or critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Overall Impact: Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five core review criteria, and additional review criteria (as applicable for the project proposed).

Key Points

Overall Impact

- Overall Impact is not a sixth review criterion.
 - Reviewers will write a paragraph summarizing the factors that informed their Overall Impact score. This paragraph is not intended to be a summary and/or restatement of the strengths and weaknesses outlined in the critique. Rather, this paragraph should succinctly inform the reader (e.g., the applicant, program staff, members of council) of the underlying rationale for the Overall Impact score in consideration with the scored review criteria.
 - Overall Impact is not necessarily the arithmetic mean of the scores for the scored review criteria.
- Overall Impact takes into consideration, but is distinct from, the scored review criteria.
- Overall Impact is the synthesis/integration of the five review criteria that are scored individually and the additional review criteria which are not scored individually.

- To evaluate, the reviewer(s) make an assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the scored review criteria, and additional review criteria (as applicable for the project proposed).
 - Likelihood (i.e., probability) is primarily derived from the investigator(s), approach and environment criteria.
 - Sustained powerful influence is primarily derived from the significance and innovation criteria.
 - Research field(s) may vary widely, so it would be helpful if reviewers identify in their reviews the research field(s) they believe will be influenced by each project.

Question: What should be included in the Overall Impact paragraph?

Answer: The Overall Impact paragraph provides the reviewer with the opportunity of explaining how the Overall Impact score was derived (i.e., those factors that contributed to the score). If a project has a strong/weak Overall Impact score then the reviewer should highlight those scored criteria that contributed to the favorable/poor score. For example, if the potential significance of a study was so great as to overshadow a number of methodological weaknesses then this should be clearly stated. Likewise, if the design of the study is so flawed as to negate any potential significance and/or innovation of the study then this should be clearly stated. Importantly, the Overall Impact paragraph should provide a clear justification of those key factors that led to his/her Overall Impact score. It is not intended to simply summarize and/or restate the strengths and weaknesses detailed in the critique.

Significance

- Significance is evaluated and scored independently of the evaluation and scoring of Investigator(s), Innovation, Approach and Environment.
- The evaluation of significance assumes that the “aims of the project are achieved” and/or will be “successfully completed.”
 - Moreover, reviewers should evaluate the significance of the project within the context of a (research) field(s). For example, autism is a significant field of study but not all studies(projects) of autism are significant.
 - Research field(s) may vary widely, so it would be helpful if reviewers identify in their reviews the research field(s) within which the project addresses an important problem or critical barrier to progress.
 - The research field may be focused on a specific basic research area (enzymology) or a specific disease (e.g., autism), or may be more broadly defined to cut across many health issues (e.g., language training, psychology).

Frequently Asked Questions

Frequently Asked Questions are available at the [Enhancing Peer Review](http://enhancing-peer-review.nih.gov/training_communication.html) website (http://enhancing-peer-review.nih.gov/training_communication.html).

Case Studies

- Case studies are intended to provide further clarity on the distinction between Significance and Overall Impact.
- They are not meant to be comprehensive or to be interpreted literally.
- Rather, they are intended to provide a conceptual framework for how to think about Significance and Overall Impact.
- Case studies are available at the [Enhancing Peer Review](http://enhancing-peer-review.nih.gov/training_communication.html) website (http://enhancing-peer-review.nih.gov/training_communication.html).

What this means:

Many applicants ask, “What is ‘impact,’ and how can I show it in my proposal?” And as stated earlier, investigators frequently are confused by the difference between “significance” and “impact.”

Essentially, NIH has instructed reviewers to evaluate significance by asking, “If all of your experiments work, then how important will your results be?” The big picture in reviewers’ minds is whether the research is worth doing.

Impact, on the other hand, includes the likelihood that the experiments will succeed. If they do not work, then there will not be any impact, even if the research is highly significant.

NIH has provided a few case studies to illustrate the difference between Overall Impact and Significance:

Case Studies

- The following case studies are intended to provide further clarity on the distinction between Significance and Overall Impact.
- They are not meant to be comprehensive or to be interpreted literally.
- Rather, they are intended to provide a conceptual framework for how to think about Significance and Overall Impact.

Case Study #1:

An investigator proposes using a novel method of viral vector-mediated siRNA delivery to knock-down the gene for a particular CNS receptor subtype in specific brain regions he/she hypothesizes to be involved in cognitive aspects of a rare mental illness. He/she proposes to use this method to examine disruption of this receptor subtype on cognitive performance in three animal models of the illness.

Scenario 1:

A. Reviewer 1 is an expert on research of the rare mental illness. He argues that the PI has previously confirmed the proposed hypothesis using pharmacological and genetic approaches. This reviewer felt that the successful accomplishment of the proposed aims would very minimally advance knowledge in the field of study devoted to the rare mental illness.

Thus, Reviewer 1 feels the application is of low significance. Reviewer 1 notes that the proposed method is highly innovative, that the models used are appropriate, and that the investigator and environment are strong. Nevertheless, in light of the low Significance of the proposal, Reviewer 1 feels the Overall Impact would be modest and scores accordingly.

- B. Reviewer 2 is an expert on viral vector-mediated siRNA delivery methods. He disagrees that the project's significance is low. He concedes that the proposed hypothesis has already been confirmed in the investigator's previous work. He argues, however, that the proposed technique is highly innovative and if successful, has the potential not only to transform the way scientists manipulate receptor function in the laboratory, but also has potential to provide the foundation for clinical application for many diseases. He suggests that the proposed replication of previous findings is actually a strength because it would confirm the successful implementation of the highly innovative methods. Thus, on the basis of the work's potential to transform technical capability and shape clinical practice in the future, Reviewer 2 argues that the application has high Significance. On the basis of high Significance and strengths in the other review criteria, Reviewer 2 believes the Overall Impact should be rated as high.

Scenario 2:

Both reviewers agree that the application addresses an important problem and that the hypothesis and methods are highly innovative. They believe that if the proposed aims were achieved, the project would significantly advance knowledge in the field and promote substantially new research directions in research on the rare mental illness as well as the broader field of mental health. Therefore, they rate Significance as high. They have strong reservations, however, about the application relative to other review criteria. The investigator and his/her colleagues do not appear to have the relevant training and expertise to successfully accomplish the work and there are some flaws in the approach that may reflect their inexperience with critical methods. Therefore, they rate the Overall Impact as moderate.

Case Study #2:

An application proposes to disrupt a well-known signal transduction pathway in mice and see if it results in an increased incidence of a particular type of breast cancer in mice.

Significance: Breast cancer is an important disease in women. However, that alone is not sufficient to say that this project has high significance. The reviewers should evaluate whether this proposed project addresses an important problem in breast cancer or a critical barrier to progress in breast cancer research. For example, will research on this signal transduction pathway in mice advance the concepts, methods, technologies, etc, related to studies of human breast cancer?

- Although breast cancer is a very important disease, the reviewers need to address whether the proposed signaling pathway and the work in mice will be important for understanding, treating, or preventing human breast cancer.
- If the signaling pathway under study is also important in another disease, such as colon cancer, the Significance might be higher, since the results of the project will be more broadly applicable.
- A project that addresses a slow growing type of breast cancer that responds well to existing therapies/treatments would be of lower significance because it is less likely to change clinical practice.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field?

- If the proposed work in mice will strongly predict what is happening in humans, the investigators are highly qualified, the environment is strong, the approach to disrupting the pathway is innovative, and the approach is flawless the project may be likely to have high Overall Impact.
- Even if the pathway and the mouse model are very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the approaches are sound, if the proposed work is not innovative or is confirmatory and duplicates many other published reports, the Overall Impact of the project on breast cancer research might be only moderate to low.

- Even if the topic is very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the project is innovative, the approach may be flawed, reducing the chance of generating useful data, which would reduce the likely Overall Impact on breast cancer research.
- Even if this project is very innovative, well conceived, and likely to have high overall impact, a subsequent project to clone and characterize receptor subtypes for this family of signal transduction molecules may be viewed as having less Overall Impact, since it might not be as innovative. Conversely, such a project might be viewed as having a greater Overall Impact, since the work is essential to develop a new drug treatment for breast cancer.

Case Study # 3:

An application proposes to develop and test an antidote for a chemical agent in an animal model.

Significance: The potential use of chemical agents in wars or related to terrorist activities is of national security concern. However, the significance of the project depends on how the project will contribute to the development of effective therapeutic agents and/or change therapeutic approach.

- Although such agents may directly affect a very limited number of individuals and the therapeutic agent(s) may have no other uses, the project has the strong likelihood of yielding life saving therapeutic agents should an exposure occur; thus the significance is very high.
- However, if well established clinical practices and multiple effective antidotes are widely available, contribution to the field of development therapeutics for chemical agent exposure will be lower and significance diminished.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field?

- The project resolves an unmet need; there are no effective therapies for this chemical exposure with high mortality. The reviewers might note the highly qualified investigators, flawless methods, an excellent animal model, and therapeutic compounds that will work on various chemical agents - High Overall Impact.
- While other therapeutic agents exist, the proposed compounds have numerous advantages in terms of side effect, ease of use and efficacy and will likely be the treatment of choice - High Overall Impact.
- The project contributes to the enhancement of the therapeutic arsenal but will not result in major changes to current clinical/therapeutic practices - Medium Overall Impact.
- While the idea is significant and sound, methodologies are flawed and investigators have very limited experience in the field. The probability of achieving the goals is low - Low Overall Impact.
- Technically sound with good investigators but the animal model has no relevance to human condition - Low Overall Impact.



REMEMBER:

There is no magic formula reviewers use to equate your individual criterion scores to your Overall Impact score.

NIH has instructed reviewers to weigh all of the individual core criteria — innovation, significance, approach, environment and investigators — when examining your application and arrive at an overall impact score. Unfortunately, there is no magic formula reviewers use to equate your individual criterion scores to your overall impact score. Each will likely rate each criterion differently. Some will base your impact score almost entirely on your experimental approach, as they did under the former application review process. Others will be much more concerned with Innovation and Significance.

The specific grant you are seeking will also affect your Overall Impact score. For an R01, reviewers likely will base the Impact score more on Environment and Approach, whereas an R21 Impact generally should depend more upon Innovation and Significance.

Integrate Impact Throughout

There is no template for incorporating Overall Impact into your grant application. For example, there is no section called “Overall Impact,” and NIH does not incentivize investigators to add a paragraph labeled as such to their proposals. Instead, the agency’s Office of Extramural Research indicates that applicants should describe impact clearly in whatever words are relevant to their proposed projects.

Some reviewers state that the impact should “bubble up” throughout the entire application. Others note that you should integrate it so that your Approach supports your Specific Aims, indicating that you will obtain useful data.

Essentially, reviewers want to see that not only are you addressing a timely and important problem, but also that you can accomplish it in the period outlined with the resources requested. Plus, the information you glean will be useful by the next generation of experiments or possibly be translatable in the near term.

With this in mind, one tactic is to include a simple “impact statement” in each of the five core criteria sections. For example, in the innovation section, you might note how your research will affect future efforts in the field, such as the following:

“The work will define future vaccine design because scientists and manufacturers will know that both IgG and IgA antibodies are required to prevent infection.”

The Project Summary/Abstract is also a good place to indicate your research’s impact because it is one of the first elements of your application reviewers will read. For instance, consider the following:

“The end product will be an affordable, accurate blood test for early detection of colon cancer without colonoscopy. Successful demonstration of this approach in colon cancer will enable application to other cancers in need of early detection biomarkers. Future directions of this research also include the application of a systems biology approach to the large datasets generated in the discovery phase to provide new insights about the earliest stages of colon cancer.”

Although NIH does not require — or even suggest — that you include such a statement, making your Overall Impact readily accessible for reviewers can support your chances that they will more easily recognize it.



STRATEGY:

One tactic is to include a simple “impact statement” in each of the five core criteria sections.

Cite Your Bibliography and References

Direct from NIH:

Provide a bibliography of any references cited in the Project Narrative. Each reference must include the names of all authors (in the same sequence in which they appear in the publication), the article and journal title, book title, volume number, page numbers, and year of publication. Include only bibliographic citations. To attach a document for Bibliography and References Cited, click Add Attachment.

Unless otherwise noted in an FOA, this section is required for submissions to NIH and other PHS agencies. This section should include any references cited in Section G.400 - PHS 398 Research Plan Form. When citing articles that fall under the Public Access Policy, were authored or co-authored by the applicant and arose from NIH support, provide the NIH Manuscript Submission reference number (e.g., NIHMS97531) or the PubMed Central (PMC) reference number (e.g., PMCID234567) for each article. If the PMCID is not yet available because the Journal submits articles directly to PMC on behalf of their authors, indicate “PMC Journal – In Process.” A list of these journals is posted at: http://publicaccess.nih.gov/submit_process_journals.htm.

Citations that are not covered by the Public Access Policy, but are publicly available in a free, online format may include URLs or PubMed ID (PMID) numbers along with the full reference (note that copies of publicly available publications are not accepted as appendix material). The references should be limited to relevant and current literature. While there is not a page limitation, it is important to be concise and to select only those literature references pertinent to the proposed research.

What this means:

Essentially, NIH reviewers do not want to be inundated with copies of articles that they can review online. So if you refer to published studies or information in your Research Strategy section, then you should cite them in this section. And unless the publication is not available online or is not part of the NIH or Pubmed system, you should not include a copy of it with your application.

If you must include a publication with your application, you should offer it as an appendix rather than including it within the application.

Here is a sample of how your bibliography entries might appear:

1. Kowal J, Tkach M, Théry C. Biogenesis and secretion of exosomes. *Curr Opin Cell Biol.* 2014 Jun 21;29C:116-125. doi: 10.1016/j.ceb.2014.05.004. [Epub ahead of print] Review. PMID: 24959705 [PubMed - as supplied by publisher]
2. Revenfeld AL, Bæk R, Nielsen MH, Stensballe A, Varming K, Jørgensen M. Diagnostic and Prognostic Potential of Extracellular Vesicles in Peripheral Blood. *Clin Ther.* 2014 Jun 1;36(6):830-846. doi: 10.1016/j.clinthera.2014.05.008. Review. PMID: 24952934 [PubMed - as supplied by publisher]
3. Lamichhane TN, Sokic S, Schardt JS, Raiker RS, Lin JW, Jay SM. Emerging roles for extracellular vesicles in tissue engineering and regenerative medicine. *Tissue Eng Part B Rev.* 2014 Jun 23. [Epub ahead of print] PMID: 24957510 [PubMed - as supplied by publisher]

CONCLUSION

Because the Research Strategy section of your application includes the Significance, Innovation and Approach criteria that NIH reviewers will use to evaluate your proposal, you will spend most of your writing time on this material. At the same time, your project's Overall Impact score will likely depend heavily on this material as well.

As if that were not enough pressure, the agency has limited the number of pages you can use for your efforts. Nonetheless, you must demonstrate not only that you have a viable proposal worth funding, but that it is a valuable addition to your scientific field. ■

Chapter 5: Special Considerations

When outlining your project, if you plan to use human or animal test subjects — or sample or data from them — you must complete the key portions of the application associated with these groups.

Both you and your institution must assure NIH that human and animal test subjects will be protected. NIH cannot award any grant until such assurances are on file with the agency.

Include enough information so reviewers will have no questions about what you propose to do. In addition, your research plan must be certified by your institutional review board (IRB) prior to funding. Although you do not need IRB approval when you submit your application, you should begin the approval process early because revisions and final approval can take time.

And before NIH can fund your grant application, there must be a Human Subject Assurance on file with the Office of Human Research Protections. This is usually handled at the institutional level.

Similarly, for proposed research using vertebrate animals, there is specific information you must include regarding the animals' treatment and the rationale for including them. Also, an institutional animal care and use committee (IACUC) must review and approve your proposal before you submit it. At NIH, an Animal Welfare Assurance must be on file with the Office of Laboratory Animal Welfare (OLAW).

INFORMING REVIEWERS ABOUT HUMAN SUBJECTS

Early on NIH’s application, you must indicate whether your proposal involves using human subjects. If it does, you must later upload several separate documents indicating who will be involved, why, how they will be impacted and your rationale for including them.

In fact, there are four such documents you must prepare:

- Protection of Human Subjects
- Data Safety Monitoring Plan
- Inclusion of Women and Minorities
- Inclusion of Children



REMEMBER:

NIH does not place any page count restrictions on the human subjects documents, but it states that you should “be succinct.”

NIH does not place any page count restrictions on these, but it states that you should “be succinct.” Do not use this section to circumvent the Research Strategy section’s page limit.

Each of these documents must include specific information regarding the human subjects, and we will look at them individually.

Protection of Human Subjects

This portion contains at least four sections, and NIH suggests you use subheads to delineate them. Further, if your research includes a clinical trial, you should have an additional subheading, “Data and Safety Monitoring Plan,” which we will discuss next.

Direct from NIH: Supplemental Grant Application Instructions:

4.1.1 Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

- Describe and justify the proposed involvement of human subjects in the work outlined in the Research Strategy section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
- Describe and justify the sampling plan, including retention strategies and the criteria for inclusion or exclusion of any subpopulation.

- If relevant, explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that ‘prisoners’ includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, provide details about all planned interventions such as dose, frequency, and administration.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

b. Sources of Materials

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, and/or data will be collected, managed, and protected as well as any individually identifiable private information will be collected specifically for the proposed research project.

c. Potential Risks

- Describe all the potential risks to subjects posed by participation in the research (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research. When alternative treatments or procedures are possible, the rationale for the proposed approach should be clear.

What it means:

Risks to Human Subjects. When you write this section, NIH suggests that you break it up into three components:

Human Subjects Involvement, Characteristics and Design. According to NIH, you should use this section to describe and justify the following:

- The proposed involvement of human subjects in the work outlined in your Research Strategy section.
- The characteristics of the subject population, including their anticipated numbers, age range and health status if relevant.
- The sampling plan, retention strategies and the criteria for including or excluding any subpopulation.
- If applicable, the rationale for involving special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners or institutionalized individuals.
- If relevant, the procedures for assigning individuals to a study group, including all details on selecting an intervention's dose, frequency and administration.
- Any collaborating sites where human subjects research will be performed and the role of those sites and collaborating investigators in performing the proposed research, including how data from the site(s) will be obtained, managed and protected.

Sources of Materials. For this section, indicate the following:

- The research material obtained from living individuals, such as specimens, records or data.
- Any data that will be collected from human subjects for the project(s) described in the application.
- Who will have access to individually identifiable private information about human subjects.
- How the specimens, records and/or data will be collected, managed and protected as well as whether any individually identifiable private information will be collected specifically for the proposed project.

Potential Risks. Here, you must detail the following:

- All the potential risks to subjects — physical, psychological, financial, legal or other — and their likelihood and seriousness to the human subjects.
- Where appropriate, any alternative treatments and procedures, including any risks and potential benefits, to participants in the proposed research. If alternative treatments or procedures are possible, clearly state the logic of your proposed approach.

For example, this section might read as follows:

Human Subjects Involvement and Characteristics: The focus of this study is to develop biomarkers of pregnancy over gestation and at the development of preeclampsia. Pregnant women (who are classified as a vulnerable population), comprise most of the study population. Because the study is about pregnancy, men are not eligible to be participants, except for control plasma.

Women would be approached in a manner consistent with university, state, and federal guidelines. The characteristics of their backgrounds are anticipated to reflect that of our patient populations. We will follow study eligibility criteria in a manner consistent with university, state, and federal guidelines.

Sources of Research Materials: As specified in the study protocol, research materials will involve medical records, pregnancy outcome data, data from research visits and examinations, newborn anthropomorphic examination, and biological samples (e.g., maternal blood, placental tissue, and umbilical cord blood).

Potential Risks: It is routine practice in the U.S. for women to undergo screening for high blood pressure and development of preeclampsia.

Risks associated with blood draw include patient discomfort (pain), bruising, inconvenience, and increased risk of infection. These risks are minimal.

Given that women and their unborn children are vulnerable subjects, our IRB requires assurance that these risks are a “*not greater than minimal risk.*” The university Committee for Protection of Human Subjects requires completion of a *Pediatric Risk Assessment Form* by an independent physician “*with expertise in pediatric population.*” Potential risks will be described in non-medical terms in the research consent form.

Direct from NIH: Supplemental Grant Application Instructions:**4.1.2 Adequacy of Protection Against Risks*****a. Recruitment and Informed Consent***

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. When appropriate, describe how potential adult subjects' capacity to consent will be determined and plans for obtaining consent from a legally authorized representative for adult subjects not able to consent.
- If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. Protections Against Risk

- Describe planned procedures for protecting against or minimizing all potential risks identified, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Describe how proposed research involving vulnerable populations meets the additional regulatory requirements, described in the HHS regulations, Subparts B, C or D. Refer to HHS regulations, and OHRP guidance:
 - Additional Protections for Pregnant Women, Human Fetuses and Neonates: <http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#subpartb>
 - Additional Protections for Prisoners: <http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#subpartc>
 - OHRP Subpart C Guidance: <http://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/prisoner-research/index.html>
 - Additional Protections for Children: <http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#subpartd>
 - OHRP Subpart D Guidance: <http://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/children-research/index.html>

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (see definition of “clinical trial” under Part III Section 3) must include a separate attachment describing the plan for data and safety monitoring of clinical trials and adverse event reporting to the IRB, the DSMB (if one has been established for the trial), the NIH and others, as appropriate, to ensure the safety of subjects. (see Part II Section 4.1.5 below).
- Where appropriate, describe plans for handling incidental findings that may be uncovered as a result of the research, such as incidental findings from research imaging, results of screening tests, or misattributed paternity

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

What it means:

Adequacy of Protection Against Risks. For this area of the document, NIH outlines these two sections:

a. Recruitment and Informed Consent. Here, provide the following information:

- Plans for recruiting subjects (where appropriate) and the process for obtaining informed consent. If your project will use children, outline the process for meeting parental consent and child assent requirements.
- Describe the circumstances under which you will seek and obtain consent, who will seek it, what information you will provide to prospective subjects and how you will document consent. When appropriate, describe how you will determine the adult subjects’ capacity to consent and plans to obtain consent from a legally authorized representative for an adult subject that is unable to consent.

- If you will seek a waiver of some or all of the informed consent elements, provide justification for the waiver.

b. Protections Against Risk. In this section, NIH states that you should include the following:

- Description of planned procedures for protecting against or minimizing *all* potential risks, including risks to the privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Describe how the research involving vulnerable populations meets HHS regulations.
 - Additional protections for pregnant women, human fetuses and neonates.
 - Additional protections for prisoners.
 - Additional protections for children.
- When appropriate, plans for ensuring necessary medical or professional intervention if subjects suffer an adverse effect. If your proposal involves a clinical trial(s) — such as biomedical or behavioral intervention studies — you must include a separate attachment of the plan for data and safety monitoring of clinical trials and adverse event reporting to the appropriate organization(s) to ensure the subjects' safety.
- Where appropriate, describe plans for handling incidental findings that are found as a result of your research.

Here's an example of how this section might read:

Recruitment and Informed Consent: Prior to implementation, we will train all research and any clinic personnel involved in recruitment for our project. Informed consent will be obtained in a method consistent with university, state, and federal regulations. A HIPAA waiver will be sought to allow the ability to screen clinic charts and/or other medical records, and then eligible women will be approached by research staff. Written study materials including brochures, flyers, and signs will be employed to provide information regarding the study. Trained researcher staff will approach eligible women and explain the study, review the consent documents, and answer questions as appropriate. All written material is presented in both English and Spanish. For those languages not spoken by the immediate staff, the clinics have access to an interpreter hotline.

If interested in participating, women will receive an IRB-approved Patient Information and Consent Form that describes the study and the terms of potential participation in the study. If a woman chooses to participate, she will sign the consent form as will the person seeking consent. A copy of the informed consent form will be given to the enrolled subject, placed in medical records charts (hospital or clinic), and in a research chart. All subjects will have the option of withdrawal from any study at any time.

Protection From Risk: With respect to protections for pregnant women, fetuses, and neonates, this project meets definitional and procedural criteria and requirements as outlined in 45 CFR 46 (§46.201-§46.204). Safeguards will be built into our plan to minimize any risks, including those associated with loss of confidentiality. Materials will be stored in a protected location with access limited to research personnel.

All research personnel will also comply with all IRB and OPRR educational programs and guidelines.

Subject data, when transmitted, will be identifiable only by a study subject number. Only personnel with a need to know will have access to any study information, an access that will require security passwords. All hard copies of subject data will be kept in locked file cabinets in the co-investigator's research office.

The university requires that all investigators and members responsible for the design and/or conduct of research provide evidence of adequate training to maintain IRB approval of a study. All individuals who will be involved in conduct of the research have completed (or will complete) the course required by the university for those who will participate in human subjects' research.

Direct from NIH: Supplemental Grant Application Instructions:

4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

Please note that financial compensation of subjects should not be presented as a benefit of participation in research.

What it means:

Potential Benefits of the Proposed Research to Human Subjects and Others.

For this section, you should provide the following information:

- The potential benefits of the research, not only to participating human subjects, but also to others.
- Why the risks to subjects are reasonable compared to the anticipated benefits to research participants and others.
- Financial compensation should not be presented to subjects as a benefit to participate in the research.

This section might read as follows:

There may be no direct and immediate benefit to the subjects from their participation in this research study. Preliminary findings from the study will be made available to researchers, as well as the general public as soon as possible. There is likely no direct benefit for the patients, except that in the future, this noninvasive assay might help diagnose preeclampsia earlier in gestation.

Direct from NIH: Supplemental Grant Application Instructions:

4.1.4 Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

What it means:

Importance of the Knowledge to Be Gained. For this portion, NIH states that you should provide details regarding the following:

- The importance of the knowledge gained or to be gained as a result of the proposed research.
- Why the risks to subjects are reasonable when compared to the importance of the expected resulting knowledge.

The following is an example of this section:

Our goal is to develop biomarkers that are windows on the physiologic world of gestation and preeclampsia. We believe this study will provide important data as to whether a flow cytometric approach will work in the setting of preeclampsia. Thus, we believe the potential risks to study subjects are limited to the risk associated with a blood draw and are appropriate for the knowledge to be gained.

Direct from NIH: Supplemental Grant Application Instructions:

4.1.5 Data and Safety Monitoring Plan

The NIH Data and Safety Monitoring Plan Policy is described and referenced in Part II Section 5.3. (Take note that ‘Data Safety Monitoring Plan’ is a new attachment added to the PHS 398 Research Plan page of FORM D applications, and are required for all proposal received after May 25, 2016.)

If the proposed research includes a clinical trial (See definition of “clinical trial” under Part III Section 3), create a document entitled “Data and Safety Monitoring Plan.” For all clinical trials, NIH requires a data and safety monitoring plan (DSMP) that is commensurate with the risks of the trial and its size and complexity. In this attachment, you must provide a description of the DSMP that you are proposing to establish for each clinical trial proposed, including:

- The overall framework for safety monitoring and what information will be monitored.
- The frequency of monitoring, including any plans for interim analysis and stopping rules (if applicable).
- The process by which Adverse Events (AEs), including Serious Adverse Events (SAEs) such as deaths, hospitalizations, and life threatening events and Unanticipated Problems (UPs), will be managed and reported as required to the Institutional Review Board (IRB), the person or group responsible for monitoring, the funding IC, the NIH Office of Biotechnology Activities (OBA; <http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>), and the Food and Drug Administration (FDA; <http://www.fda.gov/>).

- The individual(s) or group that will be responsible for trial monitoring and advising the appointing entity. Because the monitoring plan will depend on potential risks, complexity, and the nature of the trial, a number of options for monitoring are possible. These include, but are not limited to, monitoring by a:
 - PD/PI: While the PD/PI must ensure that the trial is conducted according to the protocol, in some cases (e.g., low risk trials, not blinded), it may be acceptable for the PD/PI to also be responsible for carrying out the DSMP.
 - Independent safety monitor/Designated medical monitor: a physician or other expert who is independent of the study.
 - Independent Monitoring Committee or Safety Monitoring Committee: A small group of independent investigators and biostatisticians.
 - Data and Safety Monitoring Board (DSMB): a formal independent board of experts including investigators and biostatisticians. As noted in Part II Section 5.3, NIH requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.
 - If a DSMB is used, please describe the general composition of the Board without naming specific individuals

What it means:

Data and Safety Monitoring Plan. As stated earlier, if your proposal includes a clinical trial, NIH states that you must include a section with this subheading.

You should provide the following details in this section:

- A general description of your monitoring plan for data and safety. Describe the entity responsible for monitoring and the process by which adverse events (AEs) will be reported to your institutional review board (IRB), the funding ICO, the NIH Office of Biotechnology Activities (OBA), and the

Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations.

- The frequency of monitoring will depend on potential risks, complexity and the trial's nature. Therefore, you will have a number of options regarding monitoring trials, which can include, but should not be limited to, monitoring by a:
 - a. PD/PI (required)
 - b. IRB (required)
 - c. Independent individual/safety officer
 - d. Designated medical monitor
 - e. Internal committee or board with explicit guidelines
 - f. Data and Safety Monitoring Board (DSMB). In fact, NIH specifically requires establishing DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require them, and alternative monitoring plans may be appropriate.
- You must submit a detailed Data and Safety Monitoring Plan to your IRB and subsequently to the funding ICO for approval prior to accruing human subjects.

For instance, this section might read as follows:

This is not a clinical trial, although pregnant women will be examined, blood drawn for study, and they will receive their standard of care from the co-investigator who is a physician.

The university IRB policies outlined in our IRB Reference Manual will be followed. The privacy of all subject information will be maintained as per HIPAA requirements by de-identification of subject information. The local research team will create and maintain a confidential database on the hospital system. Only research staff is authorized entry into the hospital system on the computers that will be used for data storage. All source documents are maintained in locked files in a locked room. Appropriate firewall and virus scanning software are installed and updated routinely by the hospital and/or university support staff.

Direct from NIH: Supplemental Grant Application Instructions:**4.1.6 ClinicalTrials.gov Requirements**

Public Law 110-85 (also known as the FDA Amendments Act (FDAAA) of 2007) mandates registration and results reporting of “applicable clinical trials” in ClinicalTrials.gov. Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)).

NIH encourages registration and results reporting of ALL NIH defined clinical trials whether or not registration is required under FDAAA. On January 28, 2015, NCI published a policy requiring the reporting of final trial results in a publicly accessible manner within 12 months of the trial’s primary completion date. NIH is developing a policy (See: <https://grants.nih.gov/grants/guide/notice-files/NOT-CA-15-011.html>) to require all NIH supported trials to be registered and final data reported in ClinicalTrials.gov; the final policy about this will be published in the NIH Guide for Grants and Contracts.

When registering clinical trials in the ClinicalTrials.gov Protocol Registration System, if applicable, enter the NIH Grant Number associated with the trial in the “Secondary ID” field; include activity code, institute code and 6-digit serial number (example: R01CA123456).

Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Website (<http://prsinfo.clinicaltrials.gov/>). A unique identifier called an NCT number, or ClinicalTrials.gov registry number, will be generated during the registration process. This number should be included in all Progress Reports and publications.

The FDAAA requires:

- the registration of applicable clinical trials in ClinicalTrials.gov no later than 21 days after the first subject is enrolled,

- the reporting of summary results information (including adverse events) no later than 1 year after the completion date for registered applicable clinical trials involving drugs that are approved under section 505 of the Food, Drug and Cosmetic Act (FDCA) or licensed under section 351 of the PHS Act, biologics, or of devices that are cleared under section 510k of FDCA, and
- if an “applicable clinical trial” is funded in whole or in part by an NIH grant or cooperative agreement, grant and progress report forms shall include a certification that the responsible party has made all required submissions to ClinicalTrials.gov.

For competing (new and renewal) applications that include applicable clinical trials which require registration and results reporting under FDAAA, provide the NCT number/s in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov.

The entity responsible for registering the trial is the “responsible party”. The statute defines the responsible party as:

1. the sponsor of the clinical trial (as defined in 21 C.F.R. 50.3) (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3>), or
2. the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that “the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements” for submitting information under the law) (<https://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf>). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).

For the complete statutory definitions of “responsible party” and “applicable clinical trial”, refer to Elaboration of Definitions of Responsible Party and Applicable Clinical Trial. (See: http://grants.nih.gov/ClinicalTrials_fdaaa/definitions.htm)

The signature on the application of the Authorized Organization Representative assures compliance with FDAAA.

Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa).

What it means:

Potential Section 6: ClinicalTrials.gov Requirements.

If your application includes applicable clinical trials that require registration and results reporting under the FDA Amendments Act of 2007 (FDAAA, Public Law 110-85), you should include this section to provide the ClinicalTrials.gov registry number(s) (NCT), Brief Title(s) (which is the protocol title intended for the lay public), and the identity (name and/or organization) and contact information for the responsible party. If your proposal includes a new clinical trial or if the grant will support an applicable clinical trial that is ongoing but not yet required to register under FDAAA (that is, less than 21 days have passed since enrolling the first patient), you must clearly state in this section that the project includes an applicable clinical trial that will require registration in ClinicalTrials.gov. NIH further states that the entity responsible for registering the trial — the “responsible party” — is one of the following:

- The sponsor of the clinical trial, or
- The PI of such clinical trial if so designated by a sponsor, grantee, contractor or awardee — as long as the PI “is responsible for conducting the trial, has access to and ability to meet all of the requirements” for submitting information under the FDAAA.

Inclusion of Women and Minorities

For this Human Subjects document, you must address NIH’s policy that all agency-supported biomedical and behavioral clinical research projects must include women and members of minority groups and their subpopulations unless a clear and compelling rationale and justification that including them is inappropriate with respect to the subjects’ health or the research’s purpose.

Direct from NIH: Supplemental Grant Application Instructions:

4.2 Inclusion of Women and Minorities

Create a section heading entitled “Inclusion of Women and Minorities” and place it immediately following the “Protection of Human Subjects” section. Although no specific page limits apply to this section of the application, be succinct. This section does not take the place of considering relevant biological variables (such as sex) in the research strategy. The NIH Policy on the Inclusion

of Women and Minorities in Clinical Research is described and referenced in Part II Section 5.6. Additional information and guidance can be found at:

http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the scientifically justified inclusion (or exclusion) based on sex/gender, race, and ethnicity in NIH-defined clinical research. This section is required for all studies meeting the NIH definition for clinical research, not just clinical trials. It is important to provide a detailed plan of who will be included (and/or excluded) and how the distributions of individuals on the basis of sex/gender, race, and ethnicity are justified in the context of the scientific goals of the application. Simply stating that certain individuals will not be excluded or that individuals of either sex/gender or any race/ethnicity are eligible is not sufficient. Details about why the individuals are the appropriate individuals to accomplish the scientific goals of the study should be provided.

In this section, address, at a minimum, the following four points:

1. Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the format in the PHS Inclusion Enrollment Report. Instructions for completing this form are in the General Application Guide for NIH and Other PHS Agencies Section G.500 (See: <http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general/g.500-phs-inclusion-enrollment-report.htm>), and below in Part II Section 4.3 of these Supplemental Instructions.
2. Describe the subject selection criteria and rationale for selection of sex/gender, racial, and ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. Provide a compelling rationale for proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study.
4. Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members as subjects. This is particularly important if difficulty recruiting certain groups is anticipated.

Additional Considerations for justifying inclusion:

There may be reasons why the proposed sample is limited by sex/gender, race, and/or ethnicity. This should be addressed as part of the four points detailed above.

- Inclusion of certain individuals would be inappropriate with respect to their health;
- The research question addressed is only relevant to certain groups or there is a gap in the research area;
- Evidence from prior research strongly demonstrates no difference on the basis of sex/gender, race, and/or ethnicity;
- Sufficient data already exist with regard to the outcome of comparable studies in the excluded group(s) and duplication is not needed in this study;
- A certain group or groups is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects (e.g., uniquely valuable stored specimens or existing datasets are limited by sex/gender, race, and/or ethnicity; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens); and/or
- Representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete sex/gender documentation are used), and this does not compromise the scientific objectives of the research.
- In general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups. This should be considered when developing outreach plans. Establishing collaborations or other arrangements to recruit may be necessary.

Additional guidance for research utilizing existing datasets or resources:

- Inclusion must be addressed when conducting NIH-defined clinical research, even if the samples or data have already been collected as part of a different study. Details about the sex/gender, race, and ethnicity composition of the existing dataset/resource should be provided and justified as appropriate to the scientific goals of the proposed study.
- For the purposes of inclusion policy, an existing dataset may be

constructed of different types of data including but not limited to survey data, demographic information, health information, genomic information, etc. Also included would be data to be derived from existing samples of cells, tissues, or other types of materials that may have been previously collected for a different purpose or research question but will now be used to answer a new research question. In general, these will be studies meeting the NIH definition for clinical research with a prospective plan to analyze existing data and/or derive data from an existing resource and where no ongoing or future contact with participants is anticipated. More information about what is considered an existing dataset or resource for inclusion policy is available here: http://grants.nih.gov/grants/funding/women_min/datasets_faq.htm.

- Additional guidance on completing the PHS Inclusion Enrollment Report(s) when working with existing datasets or specimens is available under Part II Section 4.3.

4.2.1 Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If the proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also **MUST** address plans for how sex/gender, race, and ethnicity will be taken into consideration in the design and valid analysis of the trial. Valid analysis means an unbiased assessment which will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect.

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the scientifically justified inclusion plans, including these additional requirements for NIH-defined Phase III clinical trials.

- Applicants should address the following issues for ensuring valid analyses:
 - Inclusive eligibility criteria – in general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups;

- Allocation of study participants of both sexes/genders (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization;
 - Unbiased evaluation of the outcome(s) of study participants; and
 - Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex/gender, race, and/or ethnicity, particularly if prior evidence strongly suggests that differences exist.
- Applicants also should address whether they plan to test or not test for differences in effect among sex/gender, racial, and/or ethnic groups and why that is or is not appropriate. This may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies as well as observational, natural history, epidemiology and/or other relevant studies. Additional factors may include planned primary and secondary outcomes and whether there are previous studies that support or negate the likelihood of differences between groups.
 - The plans must include selection and discussion of one of the following analysis plans:
 - Plans to conduct analyses to detect significant differences in intervention effect among sex/gender, racial, and/or ethnic subgroups when prior studies strongly support these significant differences among one or more subgroups, or
 - Plans to include and analyze sex/gender, racial, and/or ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender, racial, and ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), or
 - Plans to conduct valid analyses of the intervention effect in sex/gender, racial, and/or ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups.

What it means:

Cost is not an acceptable reason for excluding women or minorities except when the study would duplicate data from other sources, NIH states.

Consequently, Scientific Review Groups (SRGs) — also known as “study sections” — will assess your application as being acceptable or unacceptable regarding the inclusion of women and minorities in clinical research.

At a minimum, NIH states that this document must address the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format. If you are using existing specimens and/or data without access to information on the distribution of women and minorities, state so and explain the impact on your research’s goals as part of the rationale that you cannot describe inclusion. Alternatively, describe the gender and minority composition of the population base from whom the specimens and/or data will be obtained.
2. The subject selection criteria and rationale for selecting sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. Include, but do not limit yourself to, information regarding the population characteristics of the disease or condition under study.
3. A compelling rationale for excluding any sex/gender or racial/ethnic group.
4. Proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.



REMEMBER:

Cost is not an acceptable reason for excluding women or minorities except when the study would duplicate data from other sources.

The following are examples of acceptable reasons to justify excluding human subjects based upon sex/gender:

1. One gender is excluded because of the following:
 - Including them would be inappropriate with respect to their health;
 - The proposal’s research question is relevant to only one gender;
 - Evidence from prior research strongly demonstrates no difference between genders; or
 - Sufficient data already exist regarding comparable studies’ outcomes in the excluded gender, and duplication is not needed in this study.
2. The research’s purpose constrains the applicant’s selection of study subjects by gender (for example, uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
3. Gender representation of specimens or existing datasets cannot be accurately determined — for instance, pooled blood samples, stored specimens or datasets with incomplete gender documentation — and this does not compromise the research’s scientific objectives.

For excluding minority groups or subgroups, the following examples show acceptable justifications:

1. Some or all minority groups or subgroups are excluded from the proposed research because of one of the following:
 - Including them would be inappropriate with respect to their health;
 - The proposal’s research question is relevant to only one racial or ethnic group;
 - Prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
 - Your proposal involves a single minority group study to fill a research gap;or

- Sufficient data already exist regarding comparable study outcomes in the excluded racial or ethnic groups, and documentation is not needed in this study.
2. The study's geographical location has only limited numbers of those minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
 - The study's size;
 - The relevant characteristics of the disease, disorder or condition; or
 - The feasibility of making a collaboration or consortium or other arrangements to include representation.
 3. The purpose of the research limits the applicant's study subject selection by race or ethnicity — for example, uniquely valued cohorts, stored specimens or existing datasets are of limited minority representation; very small numbers of subjects are involved; or overriding factors dictate subject selection, such as matching of transplant recipients or availability of rare surgical specimens.
 4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined — for instance, pooled blood samples, stored specimens, or datasets with incomplete racial or ethnic documentation — and this does not compromise the research's scientific objectives.

If your proposal includes a Phase III clinical trial, this section also must address whether you expect clinically important sex/gender and/or race/ethnicity differences from the intervention effect. This discussion may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology, and other relevant studies. Your discussion of expected sex/gender and/or race/ethnicity differences in intervention effect must include selecting and discussing one of the following:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or race/ethnic subgroups when prior studies strongly support these significant differences among subgroups; or
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups; or
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect among subgroups.

For example, this document could read as follows:

A. Inclusion of Women

The rationale for inclusion of women in this study is that preeclampsia only occurs in pregnant women. We will also recruit males in the same age and ethnic distribution as controls.

B. Inclusion of Minorities

We will increase awareness of our study among the diverse minority population at the research sites. We will strive to create a diverse research team, as a culturally diverse research staff can enhance enrollment of minorities. We will utilize our strong presence at the various outpatient clinics and offices to ensure screening and recruitment opportunities across populations. Any study materials that are created will be sensitive to the multicultural makeup of our patient population.

COMPLETE INCLUSION ENROLLMENT REPORT(S)

This form is used to report both planned and cumulative (or actual) enrollment, and describes the sex/gender, race, and ethnicity of the study participants.

Direct from NIH: Supplemental Grant Application Instructions:

4.3 Instructions for Completing the PHS Inclusion Enrollment Report(s) for Sex/Gender, Race, and Ethnicity

The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described in Part II Section 5.6. The NIH Policy on Reporting Race and Ethnicity Data for Subjects in Clinical Research is described and referenced in Part II Section 5.7.

Instructions for Completing PHS Inclusion Enrollment Reports

For electronic SF424 (R&R) applications using the Forms D package, if your application includes PHS Inclusion Enrollment Report(s), these are available as part of the SF424 application package. For paper PHS 398 applications, if your application inclusion includes the PHS Inclusion Enrollment Report(s), these will be inserted after the section describing plans for the inclusion of women and minorities. (See General Application Guide for NIH and Other PHS Agencies: <http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general/g.500-phs-inclusion-enrollment-report.htm>, Section G.500 for electronic applications using Forms D; <http://grants.nih.gov/grants/funding/phs398/phs398.html> for paper applications for more information).

In addition to providing inclusion plans (per Part II Section 4.2), applicants are instructed to provide the distribution of participants by sex/gender, racial, and ethnic categories using the PHS Inclusion Enrollment Report(s). See below for additional guidance on how to complete the PHS 398 Inclusion Enrollment Report form.

When Completing each PHS Inclusion Enrollment Report(s)

- See the General Application Guide for NIH and Other PHS Agencies Section G.500 (<http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general/g.500-phs-inclusion-enrollment-report.htm>) for explicit instructions on completing the fields on the PHS Inclusion Enrollment Report form. In addition, see below for more information that will assist in form completion.

- **Application involves more than one study:** If the application includes more than one study, provide separate PHS Inclusion Enrollment Report for each unless otherwise directed by the Funding Opportunity Announcement (FOA). At a minimum, studies involving subjects at non-US sites (even if part of the same study) must be reported separately from studies involving subjects at US sites.
- **Multi-site studies:** If the application includes a study recruiting subjects at more than one site/location, investigators may create one PHS Inclusion Enrollment Report table or separate multiple PHS Inclusion Enrollment Report tables to enable reporting by Reports (per site), depending on the scientific goals of the study and whether monitoring of inclusion enrollment would benefit from being combined or separated. Please review the Funding Opportunity Announcement (FOA) to determine if there are any specific requirements about how to complete the PHS Inclusion Enrollment Report(s).
- **Multi-Project Applications:** If you are preparing a multi-project application, include the PHS Inclusion Enrollment Report(s) with the component(s) that involves the study(s) unless otherwise directed by the FOA. Should the study span more than one subproject component, include the PHS Inclusion Enrollment Report(s) with only one subproject component and insert a comment in the comment field to indicate what other subprojects components it is associated with.
 - For paper PHS 398 applications if your application involves subprojects, attach the PHS Inclusion Enrollment Report(s) to the relevant component immediately after the section describing the plans for the inclusion of women and minorities.
- **NOTE: Duplicative Inclusion Reports:** It is important that the PHS Inclusion Enrollment Report table(s) for a given study only be associated with one application and be provided only once in a given application. If submitting individual application(s) as part of a network or set of linked applications, please provide the PHS Inclusion Enrollment Report table(s) with the individual site applications unless otherwise directed by the FOA.
- **Renewal applications:** When preparing a renewal (or resubmission of a renewal), investigators should provide a narrative description regarding

the cumulative enrollment from the previous funding period(s) as part of the progress report section of the research strategy attachment in the application. The PHS Inclusion Enrollment Report form should NOT be used for this purpose. If a given study will continue with the same enrollment or additional enrollment, or if new studies are proposed, provide a new PHS Inclusion Enrollment Report for each as described in the instructions above.

- **Resubmission applications:** If inclusion enrollment tables were provided in the initial submission application and those studies will be part of the resubmission application, please complete the PHS Inclusion Enrollment Report(s) form and submit again with the resubmission application, regardless of whether the enrollment has changed or not. Also, any new (additional) PHS Inclusion Enrollment Report table(s) should also be provided.
- **Revision applications:** Provide a PHS Inclusion Enrollment Report(s) form if new studies are planned as part of the Revision and they meet the NIH definition for clinical research.

Additional Guidance Information

For additional guidance information and FAQs related to inclusion policy and inclusion data forms, please see: http://grants.nih.gov/grants/funding/women_min/women_min.htm.

What it means:

- Unless otherwise stated, each study needs its own, separate report.
- If patient recruiting is going to take place at more than one site, tabular reporting, to delineate each site, is suggested.
- Multi-project applications need an Inclusion Enrollment Report with each study component
- Each Inclusion Enrollment Report per application is provided only once in the application – do not duplicate
- For renewal applications, provide a narrative description regarding the cumulative enrollment from the previous funding period(s) as part of the progress report section of the research strategy attachment in the application – do not provide an Inclusion Enrollment Report form.
- For resubmission applications, if the form was submitted in the first submission, it needs to be provided with the resubmission.

Direct from NIH: The NIH Application Guides states:

The PHS Inclusion Enrollment Report form is used for all applications involving NIH-defined clinical research.

PHS Inclusion Enrollment Report

View Burden Statement

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number: 0925-0001 and 0925-0002
Expiration Date: 10/31/2018

*Study Title (must be unique):

* Delayed Onset Study? Yes No

If study is not delayed onset, the following selections are required:

Enrollment Type Planned Cumulative (Actual)

Using an Existing Dataset or Resource Yes No

Enrollment Location Domestic Foreign

Clinical Trial Yes No

NIH-Defined Phase III Clinical Trial Yes No

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/Not Reported	Female	Male	Unknown/Not Reported	Female	Male	Unknown/Not Reported	
American Indian/Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Report 1 of 1

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Next Report >

To ensure proper performance, please save frequently.

Study Title:

Enter a unique title that describes the study that the participants will be involved in. If there is more than one study, provide a separate Study Title for each. Follow the instructions provided in the Application Guide and the FOA regarding the Inclusion of Women and Minorities. Maximum 250 characters. This is a required field.

Delayed onset study?

Select whether the study is considered delayed onset. This generally means that a study has not been developed and cannot be described in terms of human subjects' protections and inclusion. This does NOT apply to a study that can be described but will not start immediately. Additional guidance on whether a study meets the criteria to be considered delayed onset can be found in Section 2, Scenario D of the Supplemental Instructions, Part II. If the study is delayed onset, select YES. If the study is not delayed onset, select NO. This is a required field.

If you have answered “No” to delayed onset, you must answer the following and complete the enrollment table:

Enrollment Type:

Select whether the table reflects Planned Enrollment of individuals to be recruited into the study or Cumulative (e.g., actual) Enrollment for 1) participants already recruited into the study or 2) studies using an existing dataset or resource. This is a required field.

Using an existing dataset or resource? Select whether this study involves use of an existing dataset or resource. This generally means that investigators are utilizing data from a previous study or data bank. Do NOT answer Yes for individuals previously recruited specifically for this study. For additional guidance on what is considered an existing dataset refer to Supplemental Instructions, Part II Section 4.2 and this FAQ. This is a required field.

Enrollment Location:

Select whether the participants described in the inclusion enrollment report are based at a US or non-US site. At a minimum, participants at US and non-US sites must be reported separately even if for the same study. For additional guidance on working with non-US populations refer to this FAQ. This is a required field.

Clinical Trial:

Select whether the study these participants are involved in is considered a clinical trial. This is a required field.

Agency-Defined Phase III Clinical Trial:

Select whether the study is an agency-defined Phase III clinical trial. This is a required field.

Comments:

Enter information you wish to provide about this PHS Inclusion Enrollment report. This includes but is not limited to addressing information about distinctive subpopulations if relevant to the scientific hypotheses being studied and/or a study that will have a delayed onset. Maximum 500 characters.

Racial Categories:**American Indian/Alaska Native:**

Enter the expected number of females and males (in the respective fields) who are American Indian/Alaska Native and Not Hispanic or Latino, and; enter the expected number of females and males (in the respective fields) who are American Indian/Alaska Native and Hispanic or Latino. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. These are required fields.

Asian:

Enter the expected number of females and males (in the respective fields) who are Asian and Not Hispanic or Latino, and; enter the expected number of females and males (in the respective fields) who are Asian and Hispanic or Latino. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. These are required fields.

Native Hawaiian or Other Pacific Islander:

Enter the expected number of females and males (in the respective fields) who are Native Hawaiian or Other Pacific Islander and Not Hispanic or Latino, and; enter the expected number of females and males (in the respective fields) who are Native Hawaiian or Other Pacific Islander and Hispanic or Latino. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. These are required fields.

Black or African American:

Enter the expected number of females and males (in the respective fields) who are Black or African American and Not Hispanic or Latino, and; Enter the expected number of females and males (in the respective fields) who are Black or African American and Hispanic or Latino. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. These are required fields.

White:

Enter the expected number of females and males (in the respective fields) who are White and Not Hispanic or Latino, and; enter the expected number of females and males (in the respective fields) who are White and Hispanic or Latino. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. These are required fields.

More than One Race:

Enter the expected number of females and males (in the respective fields) who identify with more than one racial category and are Not Hispanic or Latino, and; enter the expected number of females and males (in the respective fields) who identify with more than one racial category and are Hispanic or Latino. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. These are required fields.

Unknown or Not Reported:

Enter the number of females, males, and individuals of unknown/not reported sex/gender (in the respective fields) whose race is unknown/not reported and who are Not Hispanic or Latino, and; enter the number of females, males, and individuals of unknown/not reported sex/gender (in the respective fields) whose race is unknown/not reported and who are Hispanic or Latino; and enter the number of females, males, and individuals of unknown/not reported sex/gender (in the respective fields) who are of unknown/not reported race and of unknown/not reported ethnicity. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. These are required fields.

Total:

The total fields at the bottom are auto-calculated to total all racial categories for females, males and individuals of unknown/not reported sex/gender who are Not Hispanic or Latino and all racial categories for females, males and individuals of unknown/not reported sex/gender who are Hispanic or Latino. Unknown/not reported fields will only be used when reporting actual enrollment on “Enrollment Type” Cumulative. The total fields at the right are auto-calculated to total all individuals in a given racial category.

What it means:

The new form, with additional study descriptors, will replace the current Planned Enrollment Report and Cumulative Inclusion Enrollment Report form. The layout of the Inclusion Enrollment Report Form has been modified to reduce confusion about racial and ethnic information being distinct concepts. NIH has modified forms used to provide information regarding planned enrollment and actual cumulative enrollment of individuals involved in clinical research studies on the basis of sex/gender, race, and ethnicity.

- Each study needs a unique title
- Delayed onset means that the study is still in development, and cannot be described at the time of application submission.
- Are you enrolling new subjects, or will you be using previously enrolled individuals?
- Where will the enrollment come from? If both US and non-US based, report them separately
- Confirm the requirements for the study to be considered a clinical trial.

**REMEMBER:**

The NIH has redefined ‘child’ to under age 18 instead of under 21.

Inclusion of Children

The NIH has redefined ‘child’ to under age 18 instead of under 21. This will align it with the typical age of consent and perception of childhood, which will allow less confusion in implementation of inclusion policy while emphasizing children as a vulnerable population that need particular attention.

Direct from NIH: Supplemental Grant Application Instructions:**4.4 Inclusion of Children**

Create a section entitled “Inclusion of Children” and place it immediately following the section on the Inclusion of Women and Minorities. Although no specific page limits apply to this section of the application, be succinct. The NIH Policy on Inclusion of Children is referenced and described in Part II Section 5.8. For the purpose of implementing these guidelines, a child is now defined as an individual under the age of 18 years (for additional information see <http://grants.nih.gov/grants/funding/children/children.htm>).

Scientific Review Groups will assess each application as being acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of children in the proposed research project. This section is required for all studies meeting the NIH definition for clinical research, not just clinical trials. It is important to provide a detailed plan of who will be included (and/or excluded) based on age. Details about why the individuals in the given age/age range are the appropriate individuals to accomplish the scientific goals of the study should be provided.

Instructions for this item of the Research Plan **including addressing the following points:**

- Describe the age(s) or age range of all individuals to be included in the proposed study.
- Specifically discuss whether children under the age of 18 (as a whole or a subset of individuals under 18) will be included or excluded.
- The description of the plan should include a rationale for selecting a specific age range of children.
- The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.

- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 CFR part 46 Subpart D: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

Justifications for Exclusion of Children

For the purposes of this policy, individuals under 18 are defined as a child; however, exclusion of any specific age or age range group should be justified in this section. It is expected that children will be included in all NIH defined clinical research unless one or more of the following exclusionary circumstances apply:

- The research topic to be studied is not relevant to children.
- Laws or regulations bar the inclusion of children in the research.
- The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
- A separate, age-specific study in children is warranted and preferable. Examples include:
 - The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
 - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or

- Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.
- Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
- Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
- Other special cases can be justified by the investigator and assessed by the review group and the Institute/Center Director to determine if acceptable

What it means:

For this Human Subjects document, you should provide the following information regarding your proposed research's inclusion of children — which NIH defines as an individual younger than 18 years of age:

- A description of the plans to include children, or if children will be excluded from the proposed research, application or proposal, present an acceptable justification for excluding them.
- If children are included, the plan description should offer a rationale for selecting a specific age range. The plan also must describe the investigative team's expertise for working with children at the ages included, of the available facilities' appropriateness to accommodate the children, and the inclusion of sufficient children to contribute to a meaningful analysis relative to the study's purpose.

- SRGs assess each application as being acceptable or unacceptable based upon the age-appropriate inclusion or exclusion of children in the proposed research project.
- When you involve children in research, you must address additional protections placed for their safety in the Adequacy of Protection Against Risks section within the Protection of Human Subjects document.

At the same time, there are specific instances when NIH indicates you can justify excluding children — or a specific age range, such as younger than 16 years of age — from your research. Keep in mind, however, that NIH policy requires you to include children in all clinical research conducted or supported by the agency unless there are clear and compelling reasons not to include them. Here are examples of when you may exclude children from your proposal:

- The research topic is not relevant to children.
- Laws or regulations bar you from including children.
- The knowledge you seek is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. In this case, you should provide documentation of other studies justifying the exclusions.
- A separate, age-specific study in children is warranted and preferable, including such examples as:
 - a. The condition is relatively rare in children when compared to adults, meaning that you would need to make an extraordinary effort to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition; or

- b. The number of children is limited because most are already involved in a nationwide pediatric disease research network; or
 - c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children — including different cognitive, developmental, or disease stages or different age-related metabolic processes. Although this situation may justify excluding children in some instances, NIH states that you should consider taking these differences into account in your study design and expand the hypotheses you are testing or the planned interventions to allow you to include children rather than exclude them.
-
- Insufficient data are available in adults to judge potential risk in children — in which case one of the research objectives could be obtaining sufficient adult data to make this judgment. Although you generally should not include children in the initial research study group, the illness' nature and seriousness may warrant their participation earlier based upon careful risk and benefit analysis.
 - You concentrate your study designs to collect additional data on pre-enrolled adult study subjects such as longitudinal follow-up studies that did not include data on children.
 - Other special cases that you can justify and the review group finds acceptable.

INFORMING REVIEWERS ABOUT VERTEBRATE ANIMAL TEST SUBJECTS

As with human subjects, if you propose to use live vertebrate animal test subjects, NIH reviewers will evaluate how you involve them. This means you must provide additional documentation to support using the animals. Provide this as a separate document which you will upload when completing your application. the animals. Provide this as a separate document which you will upload when completing your application. This section should be a brief, yet complete, description of the animals and proposed procedures they will be subjected to. In the new FORM D, four criteria, not five, need to be addressed.

Direct from NIH:

5.5.10 Vertebrate Animals

If Vertebrate Animals are involved in the project, address each of the criteria listed below.

- Provide a concise, complete description of the animals and proposed procedures.
- The responses to the criteria below must be well-integrated with the other sections. There should be sufficient detail in the responses for peer reviewers and NIH staff to evaluate. Additional details, if any, may be included in the Research Strategy.
- Identify all project/performance or collaborating site(s) and describe activities of proposed research with vertebrate animals in those sites.
- Address the following criteria as succinctly as possible. An incomplete application will not be considered for review. It will be considered incomplete if the following criteria are not addressed.

If plans for the use of animals have not been finalized, explain when and how animals are expected to be used.

If an award is made, the grantee must provide:

- detailed information on the criteria below; and
- verification of IACUC approval.

These must be submitted to the NIH awarding office prior to the involvement of animals.

An applicable Animal Welfare Assurance will be required if the grantee institution does not have one (see Part III, Section 2.2 Vertebrate Animals for more information: <https://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/supplemental-instructions-forms-d.pdf>).

The criteria are as follows:

1. **Description of Procedures.** Provide a concise description of the proposed procedures to be used that involve vertebrate animals in the work outlined in the “Research Strategy” section. Identify the species, strains, ages, sex, and total numbers of animals by species, to be used in the proposed work. If dogs or cats are proposed provide the source of the animals.
2. **Justifications:** Provide justification that the species are appropriate for the proposed research. Explain why the research goals cannot be accomplished using an alternative model (e.g. computational, human, invertebrate, in vitro).
3. **Minimization of Pain and Distress:** Describe the interventions including analgesia, anesthesia, sedation, palliative care and humane endpoints to minimize discomfort, distress, pain, and injury.
4. **Euthanasia:** State whether the method of euthanasia is consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines for the Euthanasia of Animals. If not, describe the method and provide a scientific justification.

For additional information, see <http://grants.nih.gov/grants/olaw/VASchecklist.pdf>. Do not use the vertebrate animal section to circumvent the page limits of the Research Strategy.

In addition, there is a new Vertebrate Animals Cover Page Supplement.

PHS 398 Cover Page Supplement

View Burden Statement

OMB Number: 0925-0001
Expiration Date: 10/31/2018

1. Human Subjects Section

Clinical Trial? Yes No

*Agency-Defined Phase III Clinical Trial? Yes No

2. Vertebrate Animals Section

Are vertebrate animals euthanized? Yes No

If "Yes" to euthanasia

Is method consistent with American Veterinary Medical Association (AVMA) guidelines? Yes No

If "No" to AVMA guidelines, describe method and provide scientific justification

3. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount (\$)	*Source(s)
<input type="button" value="Add"/>		

4. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? Yes No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: <http://stemcells.nih.gov/research/registry/>. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used.

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

What has changed?

New questions:

1. Are animals euthanized? Yes/No
2. If yes, is method consistent with AVMA guidelines? Yes/No
3. If No to AVMA guidelines, describe method/provide scientific justification.

What it means:

NIH states that this section should be a concise, complete description of the animals and proposed procedures.

1. A detailed description of how you propose to use the animals in the work outlined in the Research Strategy section. Identify the species, strains, ages, sex and numbers of animals you plan to use.

Here is an example of how this section might read:

Addressing the questions proposed above will require the use of specific pathogen-free, germ-free, or gnotobiotic C57BL/6 and BALB/c wild type mice and JhD^{-/-}, RAG^{-/-}, and Thy1.1 indicator mice. Some of the mice will be purchased, but for some strains we will establish breeding colonies here. Since there has been no reported difference in the effects of the virus in male and female mice and to minimize unnecessary euthanizing in the breeding colonies, experiments will be performed using both male and female mice. Young adult mice, 4-6 weeks, will be used for most experiments. Mice will be orally inoculated with a normal gut the murine strain of the virus. At times, specified in the proposed studies, fecal samples will be collected after placing mice in specially designed stainless steel cages for four hours and blood samples collected by tail vein bleeds. A set of experiments in mice will involve isolating bone marrow cells from one mouse and retro-orbitally transferring the cells into irradiated naïve mice of a congenically matched strain (chimeric experiments) and will allow determination of critical subsets of immune cells that are responsible for the generation of virus-specific antibody. Another set of experiments will involve adoptive transfer of purified cells from one mouse to a congenically matched mouse. A series of experiments will assess the impact of microbiota on the IgA response by infection of gnotobiotic and antibiotic-treated mice. All experimentally infected mice will be housed in microisolation or gnotobiotic cages in P2 containment facilities and routinely assessed in a sentinel program. We estimate we will need approximately 800 mice per year, including breeders.

2. Justification for using the animals, choice of species and the numbers you plan to use. If animals are in short supply, costly or to be used in large numbers, provide an additional rationale regarding why you selected them and at the numbers you indicate.

For instance, this section might read as follows:

The mouse is a well-established model of virus infection that has been widely used to define the pathogenesis of the virus, the immune response, and to test potential vaccine candidates. The mouse model of this virus is the best small animal model to examine the role of different immune components in the induction of protective IgA since reagents are readily available and numerous mouse strains with immunologic defects are available to determine the role each family members plays in intestinal IgA production. Adult mice will be used to facilitate repeated sampling and because of the numbers of cells and the size of the tissues that can be recovered for cell adoptive transfer studies. The experiments have been designed to obtain the most information using the least number of animals. However, the inherent variability in performing the proposed experiments requires a repetition of at least 1-2 times with at least 5 animals per group. For studies on IgA induction and virus clearance and protection a minimum of 5 mice will be used per group. A power calculation shows that 4.5 (or 5) animals are required per group when the following assumptions are made: protection rate of treated group equals 85%, protection rate in control group equals 10%.

Statistical Analysis and Endpoints. Statistical analyses are performed using SPSS Version 7.5 for Windows (SPSS Inc., Chicago, IL). Percent reductions in shedding (protection) between groups are compared using the Man Whitney U test. Antibody titers prior to and following virus challenge within a group are compared using the Wilcoxon Signed Ranks test and between groups by using the Kruskal-Wallis test followed by the Mann Whitney U test. Trend analysis is performed by linear regression and correlation coefficients between specific immune responses. Means of responses will be calculated based on multiple experiments (2-3) including a minimum of 5-10 animals or 5-10 pools of 2-5 animals/pool. Most

groups will have 5 mice/group to optimize the possibility of obtaining statistically-significant results in each experiment after attrition and outliers. This is justified by power analysis (One-way ANOVA) on a representative experiment where responses were compared in 3 groups of mice (e.g., wild type, and two knockout mouse strains) as follows: N per Group (Power): 2 (0.407); 3 (0.795); 4 (0.746); 5 (0.988); 6 (>.99); 7 (>.99); 8 (>.99).

3. The procedures for ensuring that any animal discomfort, distress, pain and injury will be limited to that which is unavoidable. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain and injury.

Here is an example of how this section might read:

Discomfort and injury to animals will be limited to that which is unavoidable for the conduct of these experiments and analgesic, anesthetic, and tranquilizing drugs will be used where appropriate to minimize discomfort and pain to animals. Animals will be monitored daily for signs of distress including non-responsiveness, labored respiration, inability to eat, bleeding, or self-mutilation. Animals will be deeply anesthetized prior to cervical dislocation. Tail vein or retro-orbital injections of cells will be performed under mild isoflurane sedation. Restraints will be utilized during tail vein bleeding and tails will be cleansed with alcohol prior to sampling to prevent infection. The procedures using these animals will be carried out within the provision of Public Law 89-544 as amended by the Animal Welfare Act of 1970 (Public Law 91-579; DHEW Publication No. (NIH) 78-23, “Guide for the Care and Use of Laboratory Animals”; NIH Guide to Grants and Contracts, vol. 7, No. 17 (1/1/79)) and related animal welfare rules and regulations henceforth issued by the Secretary of Agriculture and/or other federal or state agencies.

5. Any method of euthanasia you plan to use and the reasons for selecting it. State whether this method is consistent with the recommendations of the American Veterinary Medical Association (AVMA) Guidelines on Euthanasia. If not, include a scientific justification for not following the recommendations.

Here, you might refer to the following example:

For euthanasia, animals will be deeply anesthetized with rodent combination anesthetic (37.5 mg/ml ketamine, 1.9 mg/ml Xylazine, 0.37 mg/ml Acepromazine) and then subjected to cervical dislocation or treated with CO₂. These methods are consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association.



REMEMBER:

If you are not sure your research will require animal test subjects, you must still complete the additional documentation.

In addition, if all or part of the proposed research involving vertebrate animals will take place at alternate sites such as project/performance or collaborating site(s), you must identify those sites and describe the activities that will take place at each.

Keep in mind that if you fail to address the four points listed above, NIH can designate your application as incomplete and defer it from the peer review round. Alternatively, your impact/priority score could be negatively affected.

If you are not sure if your research will require animal test subjects, you must still complete this additional document, NIH notes. Be sure to provide an explanation, and indicate when you anticipate you will use animals. If you win the grant, you must submit to the NIH awarding office detailed information covering the five points above and verify approval by your IACUC — all before you may involve animals in your research.

NIH Research Involving Chimpanzees

The National Institutes of Health plans to substantially reduce the use of chimpanzees in NIH-funded biomedical research and designate for retirement most of the chimpanzees it currently owns or supports. Beginning on May 25, 2016, NIH will not fund any research involving chimpanzees proposed in new or other competing projects (renewal and revisions) unless the research is consistent with the definition of “noninvasive research,” as described in the “Standards of Care for Chimpanzees Held in the Federally Supported Chimpanzee Sanctuary System” at 42 CFR part 9.

INFORMING REVIEWERS ABOUT “SELECT AGENTS”

As in the case of using human or animal test subjects, you must create additional documentation — which you will upload as a separate document — if your research involves using “Select Agents.” These are hazardous biological agents and toxins that the U.S. Department of Health and Human Services (HHS) and Department of Agriculture (USDA) identify as having the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal and plant products. You can find a list of these agents, which is maintained by the CDC and the Animal APHIS Select Agent Programs, at <http://www.selectagents.gov>.

Direct from NIH: The NIH Application Guides states:

Select Agents are hazardous biological agents and toxins that have been identified by DHHS or USDA as having the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal and plant products. CDC maintains a list of these agents. See <http://www.selectagents.gov/>.

If the activities proposed in the application involve only the use of a strain(s) of Select Agents which has been excluded from the list of select agents and toxins as per 42 CFR 73.3, the Select Agent requirements do not apply. Use this section to identify the strain(s) of the Select Agent that will be used and note that it has been excluded from this list. The CDC maintains a list of exclusions at <http://www.selectagents.gov/SelectAgentsandToxinsExclusions.html>

If the strain(s) is not currently excluded from the list of select agents and toxins but you have applied or intend to apply to HHS for an exclusion from the list, use this section to indicate the status of your request or your intent to apply for an exclusion and provide a brief justification for the exclusion.

If any of the activities proposed in your application involve the use of Select Agents at any time during the proposed project period, either at the applicant organization or at any other performance site, address the following three points for each site at which Select Agent research will take place. Although no specific page limitation applies to this section, be succinct.

1. Identify the Select Agent(s) to be used in the proposed research.
2. Provide the registration status of all entities* where Select Agent(s) will be used.
 - If the performance site(s) is a foreign institution, provide the name(s) of the country or countries where Select Agent research will be performed.
- * An “entity” is defined in 42 CFR 73.1 as “any government agency (Federal, State, or local), academic institution, corporation, company, partnership, society, association, firm, sole proprietorship, or other legal entity.”
3. Provide a description of all facilities where the Select Agent(s) will be used.
 - Describe the procedures that will be used to monitor possession, use and transfer of the Select Agent(s).
 - Describe plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).
 - Describe the biocontainment resources available at all performance sites.

If you are responding to a specific funding opportunity announcement (e.g., PA or RFA), address any requirements specified by the FOA.

Reviewers will assess the information provided in this Section, and any questions associated with Select Agent research will need to be addressed prior to award.

Attach this information as a PDF file

What it means:

If your research involves only using a strain(s) of Select Agents that has been excluded from the list, the Select Agent requirements do not apply. Nonetheless, you should use this document to identify the strain(s) of the Select Agent that you will use and note that it has been excluded from the list. You can find a list of these exclusions at <http://www.selectagents.gov/SelectAgentsandToxinsExclusions.html>

On the other hand, if the strain(s) is not currently excluded from the Select Agent list but you have applied or intend to apply to HHS for an exclusion from the list, use this document to indicate your request’s status or your intent to apply for an exclusion and provide a brief justification for the exclusion.

If any of the activities proposed in your application involve using Select Agents at any time during the project period, regardless of where the research may take

place, you must address the following three points for each research site where Select Agent research will take place:

1. Identify the Select Agent(s) you plan to use in your proposed research.
2. Provide the registration status of all entities — which NIH defines as “any government agency (Federal, State, or local), academic institution, corporation, company, partnership, society, association, firm, sole proprietorship, or other legal entity” — where you will use Select Agent(s). Even if the performance site(s) is a foreign institution, provide the name(s) of the country(ies) where Select Agent research will be performed.
3. Provide a description of all facilities where you plan to use the Select Agent(s).
 - The procedures that you plan to use to monitor possession, use and transfer the Select Agent(s).
 - Your plans for appropriate biosafety, biocontainment and security of the Select Agent(s).
 - The biocontainment resources available at all performance sites.

Here is an example of a select agent section from a successful grant application (Developing small molecule therapeutics for Ebola hemorrhagic fever virus, Principal Investigator: Amab Basu, PhD):

Select Agent

Select Agent to be used:

In vitro:

Ebola Zaire Mayinga

Ebola Sudan Boniface

Marburg Angola

In vivo:

Mouse Adapted Ebola Zaire

Guinea Pig Adapted Ebola Zaire

Organization Name registration status:

Number and expiration date: XXXXXXXXXXX-XXXX expiration XX/X/XX

The foundation is a select agent registered entity with Health and Human Services, Centers for Disease Control and Prevention (CDC) and U.S. Department of Agriculture, Animal Plant Health Inspection Service, National Select Agent Program. The foundation has been inspected by the CDC National Select Agent Program for use of HHS Select Agents and Toxins, Overlap Select Agents and Toxins and USDA Select Agents and Toxins. Per the requirements of 42 CFR 73, is approved for use of select agents at BioSafety Level 2, 3, and 4 and Animal Biosafety Level 3 and 4.

Description of Facilities:

Procedures used to monitor possession, use and transfer of Select Agent(s)

The foundation maintains an experienced and trained staff of scientists, veterinarians, research technicians and veterinary technicians available to perform studies at high biocontainment and maximum containment. These individuals have demonstrated proficiency at conducting nonhuman primate studies with the agents identified in the proposal. The BSL3, ABSL3 and BSL4 Operations and Safety Manuals specify policies, procedures, and standard operating procedures (SOP) for the safe handling of biological materials in biosafety laboratories. The policies, procedures, and SOPs comply with application federal, state, and municipal regulations and with the guidelines “Biosafety in Microbiological and Biomedical Laboratories” issued by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). Employees are trained from these manuals on each facility’s mechanical systems, biosafety, biocontainment and security. Employees are also trained according to project specific and departmental standard operating procedures.

These procedures apply to all foundation employees and visitors that use, generate, store, or dispose of potentially infectious materials in foundation biosafety laboratories and to persons who must enter those laboratories to perform services. Prior to conducting experiments in the foundation biosafety laboratories,

staff members must read and be trained in the requirements outlined in this manual and applicable task-specific safety plans.

At the present time, the director is the CDC designated Responsible Official (RO). Select agent use, transfer or possession is forbidden without the permission of the Responsible Official or Alternate Responsible Official, the required forms filed, and written approval received from the CDC Select Agent Program.

Upon approval, the BSK-3/4 Committee will consider select agents proposals for work in the BSL-3/4 laboratory. BSL-3/4-qualified investigators desiring to work on a BSL4 project must also submit a Biohazard Application to the Biohazards and Safety committee. The foundation Biosafety Committee has a key role in the foundation's overall biosafety program. The committee is responsible for evaluating the foundation's facility, equipment, and staff capabilities for performing work in a safe manner. The committee is also responsible for:

- Reviewing protocols and risk assessments submitted by principal investigators for work involving biological materials or toxins.
- Meeting with PIs prior to the implementation of projects involving biological materials or biological-derived toxins.
- Evaluating the foundation's staff, facility and equipment for their ability to provide the appropriate containment for handling biological materials.
- Assessing the foundation's compliance with existing federal, state and local environmental regulations.

Committee membership consists of representatives from technical departments, management, and administrative staff, among others. The committee communicates by e-mail with face-to-face meetings at least quarterly and/or more frequently if necessary.

Plans for appropriate biosafety, biocontainment, and security of the Select Agent(s)

Infectious cultures, inventory stocks or toxic materials are stored inside the BSL4 laboratory in refrigerators, incubators or freezers that are marked with the universal biohazard sign. Principal investigators maintain inventories of infectious agents

stocks. A master list of select agents is securely kept by Virology and Immunology in the BSL4 Scientific Manager's office. A computerize and bar code inventory system has been selected for the select agent inventory. All issues relating to select agent inventory or tracking must be directed to the Responsible Official.

All infectious or toxic materials stored in refrigerators or freezers are properly labeled and stored in containers capable of withstanding thermal shock of freezing and thawing. Each container is labeled with the identity of the infectious agents, the date of the preparation, the initials or name of the responsible laboratorian and a reference number that links the material to the more inclusive information contained in the inventory database.

When work is completed, all infectious cultures and toxins are removed from workbenches and cabinets and stored in a designated refrigerator or freezer. Materials to be discarded are placed in a sealable container filled with a suitable disinfectant. The container is placed in a discard pan containing the disinfectant. Discard pans are placed in a cart and transported to the autoclave. Labware containing infectious liquids are stored and transported in leak-proof containers large enough to contain the fluid in case of leakage.

CONCLUSION

Finally, if you are using human or animal test subjects and/or select agents, NIH wants to know how and for what. Consequently, you will have to upload specific information as part of your grant application. But be sure you do not use these documents to bypass the Research Strategy page limits. ■

Chapter 6: Budgeting Your Research

When applying for a National Institutes of Health (NIH) grant, in addition to your proposal's science, you also have to forecast how much money you will need to complete your research. Therefore, you should use the budget and associated justifications to present and support all the expenses required to achieve your proposal's objectives.

In fact, your budget's numbers are almost as important as — if not more so — the words you use to tell your research's story. This part of your application communicates to reviewers what you plan to do with the money you are asking them to invest in your project. Some reviewers even flip to the budget first to get a snapshot of the proposal and help them understand it. Although they should not take your budget into consideration as part of the assessment process, the information is available to them. And reviewers are told to evaluate the application and assign a priority score based upon the science and feasibility, and some believe the budget an indicator of feasibility.

There are two types of budget proposals that you can submit:

1. Modular budget
2. Detailed budget

You can use a modular budget for certain research grants if you request \$250,000 or less per year for direct costs. These are simplified, so you would not submit detailed categorical information with these applications. You will input details about this type of budget beginning on form PHS 398.

Detailed budgets — also called research and related (R&R) budgets — involve filling out three separate data entry screens as part of the R01 grant application. And there are a total of 11 different sections that make up the three data screens. In addition, you have to complete a separate detailed budget for each year of support you request. So this can become a rather lengthy process.

Finally, your application's budget, regardless of the type you use, also includes several justification documents. These are narratives that you construct to indicate where you propose to spend your grant-related funds and why.



REMEMBER:

Some reviewers flip to the budget first to get a snapshot of the proposal that will help them understand it.

Direct vs. Indirect Costs

For budgeting purposes, NIH makes a distinction between “direct” and “indirect” costs associated with your proposal:

- Direct costs — Those that can be specifically identified with a particular project or activity.
- Indirect costs — Also called facilities and administrative (F&A) costs, the grantee incurs these for common or joint objectives that cannot be identified specifically with a particular project or program.

When formulating a modular budget, you should consider only direct costs. For detailed budgets, however, you must include both direct and indirect costs. Keep in mind, however, that universities and other institutions commonly establish a single, negotiated contracted percentage rate to represent F&A costs for all NIH grants on their campuses, and you can obtain that information directly from your organization to include with your application’s budget.

Note: From whatever award money you are granted, your administration will “take off the top,” for itself, the F&A percentage it has negotiated with the government.

Also remember that if you have a subcontract or consortium agreement with another institution, you should treat any costs associated with that agreement as “direct,” including that subcontracted organization’s indirect costs.

STRATEGY FOR PLANNING YOUR BUDGET

The NIH application includes both R&R and modular budget components, and you can use these to continually revise and keep track of your budget's size during your application writing process. In fact, this can be a helpful tool in your budget planning process.

And the National Institute of Allergy and Infectious Diseases (NIAID) suggests that you should expect to spend time and effort crafting your thorough justification for your budget. “The more detail you include to justify it, the better — weak budget justifications are a big problem for many applications,” the Institute states.

If your budget expands beyond your grant type or career stage, you should consider cutting back your experiments or Specific Aims, experts recommend.

Also, remember that NIH allows you to use grant money for certain specific costs, and it uses the following principles to define which costs you can charge to your grants:

- **Allowable** — Also known as “conformance,” this principle centers on complying with the limitations and exclusions contained in the terms and conditions of the award, which can vary depending upon the type of activity, recipient and other characteristics of the specific grant.
- **Allocable** — You can allocate a cost to your grant if you incur it solely to advance work under the proposal, it benefits both the project and other work at your institution, or it is necessary to the overall organizational operation and is assignable to the grant at least partially.
- **Reasonable** — A cost may be reasonable if it and its associated costs reflect an action a prudent person would take under the circumstances prevailing when the decision to incur the cost was made.
- **Consistency** — You, as the Principal Investigator (PI), must consistently assign costs to cost objectives.

These four principles apply regardless of the type of budget you use.



STRATEGY:

You should ask only for enough money to do the work you propose, but do not think that a “low ball,” unrealistic budget will curry favor.

Another key aspect to your budget strategy is knowing how much money to request. As the “Goldilocks” fairytale says, “Not too much, not too little, but just right.” You should ask only for enough money to do the work you propose, but do not think that a “low ball,” unrealistic budget will curry favor. In fact, you should keep the following in mind:

- NIH reviewers search grant applications for reasonable costs and judge proposals based on whether your Specific Aims and methods support your request.
- Reviewers also read the percent effort you list for each key person and judge whether they are in sync with their expectations based upon your application.
- If you significantly over- or underestimate your budget, reviewers often take this as you not understanding your work’s scope.

Consequently, NIAID recommends that you should calculate salaries as 60 percent to 80 percent of your total budget request. When you formulate the PI’s salary, remember the mandatory cap, which changes each year. You can find the salary cap information on NIH’s Web site: http://grants.nih.gov/grants/policy/salcap_summary.htm. And do not ask for anything that might appear extravagant, such as too much travel.

You should also use your budget to mention any discounts you receive. For example, you use a large number of antibodies from a single source for your project, and that supplier gives you a 25 percent volume discount. You should note this in your budget documents because reviewers will want to know that you have established this relationship.

NIAID also recommends that you should not request funds for equipment or resources you have already listed as available in your Research and Other Related Project Information forms. If you do, reviewers will delete these items, and it may tarnish your credibility.

Alternatively, once you have determined the resources you will need for your project, identify what your institution can provide. Once you have this information, NIAID recommends that you ask the following:

- Does your institution offer you a budget for purchasing needed equipment?
- Will you have access to the necessary equipment, especially any large equipment (for instance, that costing more than \$10,000) that you can share?
- If not, is there someone with whom you can collaborate who has access to that equipment?

At the same time, if you decide to request funds for equipment as part of your budget, NIAID offers the following guidelines:

- Requesting funds for small equipment or items not usually shared is fine.
- New investigators generally should avoid asking for expensive equipment. Study sections are more likely to approve such requests once you have firmly established yourself and are in charge of a larger group.

If you find yourself needing the expensive equipment as an absolute necessity for your proposal, however, make sure it is essential and justify it well, NIAID notes. You can create a separate module for that equipment, make it a one-time cost, and do not add it to your base amount.

Also keep in mind any service contracts associated with such equipment. If NIH funds the instrumentation, the agency will want to ensure it stays functional, and this includes grant funding for service contracts. Even if you share the equipment, you also share service contracts for this equipment, and you should reflect this in your budget.

When deciding how much to ask for, experts recommend that you consider that each grant mechanism has a cap. For example, R01s have a \$250,000 yearly cap for modular budgets. And if you request \$175,000 or \$200,000 instead of \$250,000, as a new investigator, you can show reviewers that you are easing your way into the field, which could be a good thing, some experts note.

On the other hand, if you are performing human subject or animal studies, you may need the full amount because such research is expensive. Therefore, be sure to explain in your budget request the expensive nature of the animal/human testing and your type of research.

**TIP:**

When deciding how much to ask for, experts recommend that you consider that each grant mechanism has a cap.

To ensure that you include everything you should in your financial plan, some experts recommend that you have someone else review it to search for anything that you have missed. Another option is to work closely with your sponsored programs office to ensure you complete your budget section correctly.

Not a Review Criterion, But ...

Generally, NIH reviewers are not supposed to take your budget into consideration as part of the assessment process. They are there to evaluate the application and assign a priority score based upon the science and feasibility.

The budget, however, is there if reviewers wish to look at it — and many do — and factor it into their scores even though it does not appear on the official summary. After all, they say, the budget is one measure of a PI's experience and judgment.

If the reviewer considers your budget inadequate, you may be told that your proposal is “ambitious.” Although excellent science is necessary to receive a good score, that is not sufficient. NIH is equally concerned with whether you will likely accomplish the goals and milestones you lay out in your application. Less experienced investigators often will try to show that they are a “bargain,” thinking that the more “bang for its buck” the agency receives, the more impressed reviewers will be. This is not a good calculation because they usually do not care about a bargain. Instead, they care about you successfully completing the proposed study.

Moreover, less experienced investigators often think, “I’ll say what I have to in the application to get the funding. I’ll worry about actually carrying out the work after I have the money.” On that note, be careful what you wish for.

The last thing you want is to win a grant award, and then spend as many as five years trying to fulfill your commitments with inadequate resources. In particular, one place where you can easily cut your budget is the amount of effort you allocate for you and/or your co-investigators. Keep in mind, however, that this will likely leave you overwhelmed because no matter what you list as your percent effort, you still have to do or oversee all the work or end with a poorly run grant.

So if your budget is too low, you make it difficult on yourself once you are funded. And you run the risk of failing to honor your commitments to NIH, which may cost you in the long run.

Note: Many comments in this section courtesy of William Gerin, PhD, Professor of Biobehavioral Health at Pennsylvania State University.



REMEMBER:

If the reviewer considers your budget inadequate, you may be told that your proposal is “ambitious.”

CREATE YOUR BUDGET

When you create your budget, remember that reviewers often use it to judge your competence by comparing it to your project's scope.

If you are from a domestic institution and request \$250,000 per year or less in direct costs for your proposed project, you can use a modular budget. This is a simplified method for requesting funds, meaning you do not need to submit detailed categorical information with your application.

Using modular budgets, PIs request funding in \$25,000 increments. Keep in mind, however, that this funding mechanism offers no inflationary increases for future years, which requires you to plan your entire budget at the outset.

On the other hand, if you are applying for a grant from a foreign institution or for more than \$250,000, you will need to submit an R&R budget. This will require the following:

- Using the R&R budget component forms (Application Sections A-K).
- Requesting a salary below the annual cap.
- Ensuring your direct institutional costs are consistent on all budget forms.
- Using whole numbers for person months and percent effort, and dollars for costs. Rounding calculations to the nearest dollar, but institutional costs do not need to be in whole numbers.

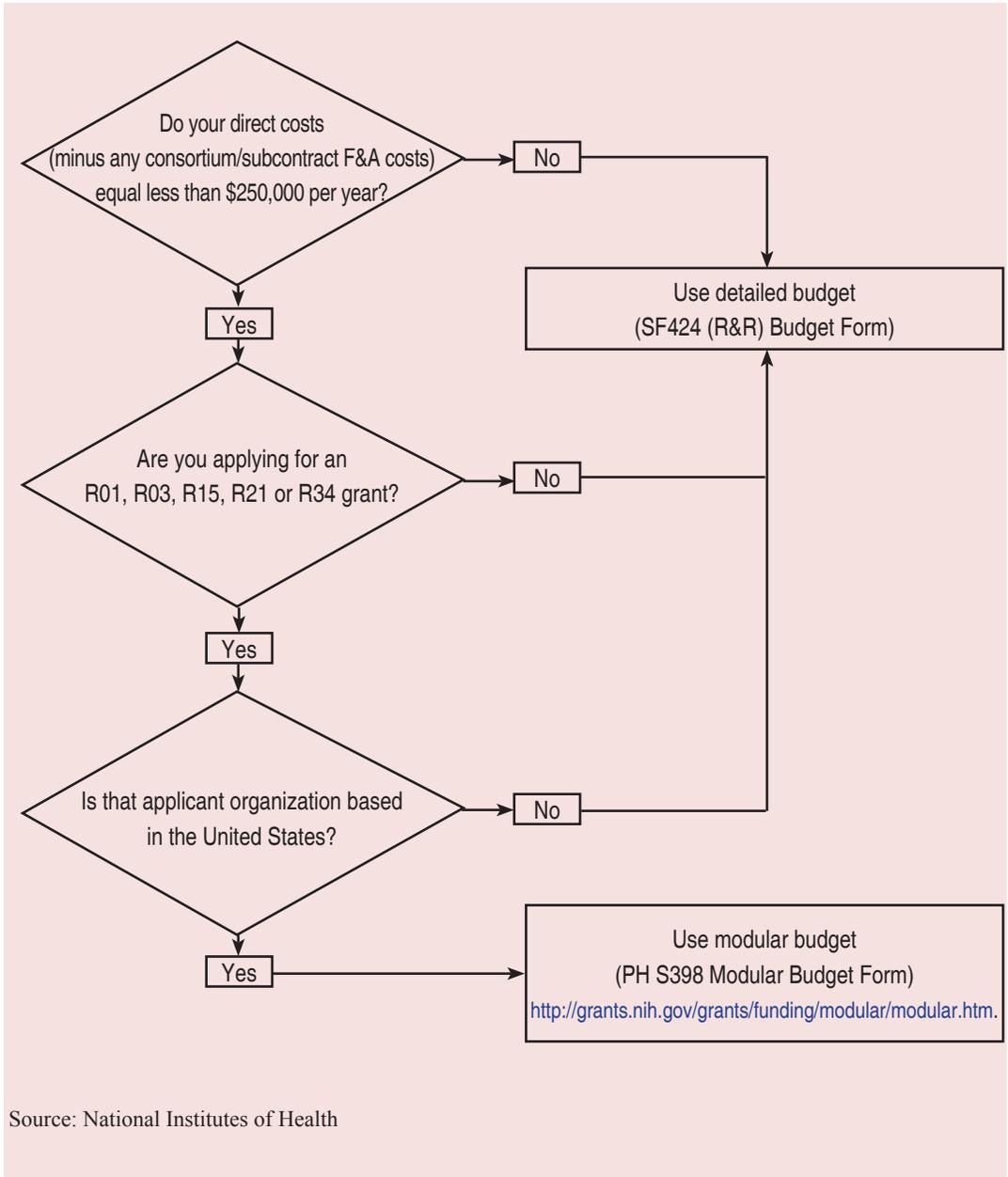


REMEMBER:

Modular budgets offer no inflationary increases for future years, which requires you to plan your entire budget at the outset.

Modular or Detailed Budget?

To determine whether you should choose a modular or R&R budget, use the following flow chart from NIH:



Source: National Institutes of Health

MODULAR BUDGETS HAVE A LIMIT

Direct from NIH: The NIH Application Guides states:

Modular budgets are applicable to certain research grant applications from domestic organizations requesting \$250,000 or less per year for direct costs. International organizations and others that do not fall under this definition should use the detailed budget forms described in Section G.300 - R&R Budget Form. Note, consortium/contractual F&A costs are not factored into the direct cost limit. They may be requested in addition to the \$250,000 limit. Modular budgets are simplified; therefore, detailed categorical information is not to be submitted with the application.

For all modular budgets, request total direct costs (in modules of \$25,000), reflecting appropriate support for the project. There will be no future year escalations. A typical modular grant application will request the same number of modules in each year. Provide an additional narrative budget justification for any variation in the number of modules requested.

What this means:

Once you have determined your budgetary needs in \$25,000 increments — not to exceed \$250,000 — you must support your monetary request. For modular budgets, you will do this by completing three narrative “justifications”:

1. Personnel Justification
2. Consortium Justification
3. Additional Justification

Some applicants might be tempted to add details of their scientific approach to the budget justifications sections to boost their chances of getting all the funding they seek. Although reviewers do carefully consider these financial planning documents, they generally are only making sure the budget is appropriate for the proposed experiments.

Therefore, details about your experimental approach are inappropriate for this section because you cannot be sure your reviewers will read it. If your approach requires something that is unusually expensive, such as lots of animal costs for a transgenic study, however, then definitely do point that out in the budget section.

Note that your budget request should not factor in your overall impact score because it is in the “other” category, which is discussed after a score is assigned. On the other hand, if reviewers think your request is excessive, they will recommend cuts. And there may be “budget envy” among some reviewers, especially if your salary structure looks high — as at a private company or national lab. Be sure to explain your salary structure in the Personnel Justification if you think that might be an issue.

Personnel Justification

Direct from NIH: The NIH Application Guides states:

List all personnel, including names, percent of effort and roles on the project. NIH and other PHS agencies use the concept of person months as a metric for determining percent of effort. To assist applicants unfamiliar with this concept, resources are available on the web at http://grants.nih.gov/grants/policy/person_months_faqs.htm. Frequently asked questions and a conversion calculator are available.

No individual salary information should be provided. Since the modules should be a reasonable estimate of costs allowable, allocable, and appropriate for the proposed project, applicants must use the current legislatively imposed salary limitation when estimating the number of modules. For guidance on current salary limitations contact your office of sponsored programs.

The salaries of administrative and clerical personnel should normally be treated as F&A costs. Inclusion of such costs may be appropriate only if all of the following conditions are met:

1. Administrative or clerical services are integral to a project or activity;
2. Individuals involved can be specifically identified with the project or activity;
3. Such costs are explicitly included in the budget or have prior written approval of the Federal awarding agency; and
4. The costs are not also recovered as indirect costs.

For all individuals classified as secretarial/clerical, in addition to the name, percent effort and role, provide a justification documenting how they meet all four conditions. NIH ICs may request additional information for these positions in order to assess allowability.

NIH grants also limit the compensation for graduate students. Compensation includes salary or wages, fringe benefits and tuition remission. This limit should also be used when estimating the number of modules. See: <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-017.html>

Save the information in a single file and click the add attachment button to complete this entry.

What this means:

For the Personnel Justification, you should list all personnel working on the project, their roles and the number of person months they will devote to the project. A “person month,” according to NIH, is the measure you should use to indicate the amount of time PIs, faculty and other senior personnel devote to your project.

To calculate person months, multiply the percentage of your effort associated with the project by the number of months of your appointment. NIH offers the following examples:

- 25% of a 9-month academic year appointment equals 2.25 person months ($9 \times 0.25 = 2.25$)
- 10% of a 12-month calendar year equals 1.2 person months ($12 \times 0.10 = 1.2$)
- 35% of a 3-month summer term appointment equals 1.05 person months ($3 \times 0.35 = 1.05$)

In addition, your personnel justification should briefly describe each person’s responsibilities in enough detail to justify the person’s level of effort. But you should not include salary information in this document. And you should include all key personnel even if you know they will be gone when the application is funded, NIH says.

Budgeting Effort Can Be Delicate Task

When budgeting effort for the PI and/or co-investigators, you should start with a pragmatic analysis. How much time will the particular investigator need to allocate to accomplish his project-related duties? Think in these terms: There are 40 hours in a standard workweek, and 20 percent effort would mean that person in theory would work on the project one full eight-hour day each week.

And there are additional considerations. For example, you plan to list a senior colleague as a co-investigator. You actually do not expect him to do much, but his well-known name will be useful perhaps as a political expedient, and you might feel awkward if you left him out. Consequently, you might list him at 5 or 10 percent effort. Also keep in mind that even at such a limited level, including such a senior-level salary on your budget could add approximately \$25,000 or more.

As for co-investigators who will do the work outlined in your proposal, you have to find the balance between what they have to do, how much you can afford and what would appear questionable to a reviewer. For instance, if you budget a co-investigator in charge of all the lab work at only 3 percent of her salary, the reviewer likely would find this unreasonable. Or if a co-investigator's main job is to help with data analysis that does not begin until Year 4, the reviewer likely would be concerned if you budget him at 20 percent effort for all five years of the grant.

To avoid this, you should determine effort allotments based upon the following criteria:

1. Actual effort as matched to the anticipated work level
2. “Political” and personal considerations
3. Funds that are available
4. Appropriateness of the effort level as perceived by reviewers.

When considering effort for consultants, you will use the budget justification section to describe not only what she will do, but also how many days per year she will spend on the project and at what fee per day. You can break the cost down by days or number of hours.

The consultant's fee will vary depending on specialty, seniority and the credentials she has. A lower-level consultant, for example, might be someone from another university with a Masters degree in psychology who will score your heart rate variability data. You might budget this person at \$30 per hour, or roughly \$250



STRATEGY:

As for co-investigators who will do the work outlined in your proposal, you have to find the balance between what they have to do, how much you can afford and what would appear questionable to a reviewer.

per day. A more senior consultant might require \$500-\$1,000 per day, depending on seniority and fame. Keep in mind that if you pay one consultant too much per day, you run the risk of a reviewer flagging your application negatively.

Follow This Example

The following is an example of a Personnel Justification taken from a successful R01 grant application (Method for Guiding Ablative Therapy of Cardiac Arrhythmias. Principal Investigator: Antonis Aroundas, PhD):

Personnel Justification:

[Dr. PI (9.6 Calendar Year person months)]: The Principal Investigator is a junior faculty at the [hospital], an independent investigator within the CVRC and an Assistant Professor. He has extensive experience in the development of biomedical signal processing algorithms and in conducting animal and human studies. He will have overall responsibility for this project. He will supervise and participate in all studies, perform data analysis, and prepare reports, manuscripts and abstracts.

[Dr. A], (Other Significant Contributor): [Dr. A] is an Attending Electrophysiologist at the [hospital] and an Instructor in Medicine. [Dr. A's] research interests are focused on making advances in catheter mapping and ablation of atrial and ventricular arrhythmias. Furthermore, he has been involved in developing novel approaches and technologies for the management of cardiac arrhythmias. He will provide hands on experience in the planning, execution and troubleshooting of the proposed animal experiments.

[Dr. B], (Other Significant Contributor): [Dr. B] is an Attending Electrophysiologist at the [hospital] and an Assistant Professor in Medicine. His research interests are largely related to catheter ablation procedures and device therapy. He will provide critical expertise and be involved in the planning phase but also to actively participate in conducting and troubleshooting in the proposed animal experiments and the data analysis and interpretation. Furthermore, his experience as an Attending Electrophysiologist will be academically valuable, both in theory and experimentally.

[Dr. C], (Other Significant Contributor), [Dr. C] is an Assistant Professor in Medicine and a Staff Electrophysiologist at the [hospital]. She is currently the Director of Interventional Electrophysiological Laboratory. She has extensive experience with catheter ablation procedures, implantation and management of pacemakers, defibrillators and cardiac resynchronization devices. She will provide valuable hands on training and guidance in planning and troubleshooting the electrophysiological experiments. She will participate and perform the catheter ablation procedures, and she will also provide support in the optimization of the electrophysiological experiments.

[Dr. D), (Other Significant Contributor): [Dr. D] is an Attending Electrophysiologist at the [hospital] and an Assistant Professor in Medicine. [Dr. D's] group has been focused on making advances in catheter mapping and ablation of atrial and ventricular arrhythmias. He is the Director of the Cardiac Resynchronization Clinic, which is involved with developing novel approaches and technologies for the management of cardiac arrhythmias. He will provide all the necessary electrophysiological equipment for the experiments and hands on experience in the planning, execution and troubleshooting of the proposed animal experiments.

Postdoctoral Fellow: to be named (12.0 calendar months effort): He or she will be involved in conducting the animal experiments and will have the day-to-day responsibility for this project.

Graduate Student, [(9.6 calendar year person months effort in Year 1, 10.8 calendar year person months effort in Years 2-4)]: [The graduate student] has worked for 6 years at [a hospital's] Cardiac Rhythm Management Division as a Clinical Engineer, Staff Scientist, and program manager before pursuing a PhD. He has extensive experience in processing intracardiac signals and assembling cardiac electrophysiology related hardware. He will have responsibility for developing the signal processing algorithms and assembling and testing the hardware for this project. He will also participate in all studies and the data analysis.

Consortium Justification

Direct from NIH: The NIH Application Guides states:

Provide an estimate of total costs (direct plus Facilities and Administrative) for each year, rounded to the nearest \$1,000. List the individuals/ organizations with whom consortium or contractual arrangements have been made. List all personnel, including percent of effort, using the metric of person months (http://grants.nih.gov/grants/policy/person_months_faqs.htm), and roles on the project. No individual salary information should be provided. Indicate whether the collaborating institution is foreign or domestic. While only the direct cost for a consortium/contractual arrangement is factored into eligibility for using the modular budget format, the total consortium/contractual costs must be included in the overall requested modular direct cost amount.

Attach this information as a PDF file.

What this means:

Consortiums are agreements between the applicant and a collaborator, which can be an individual or an organization, to carry out a portion of the grant-supported research. If you receive an NIH grant, you will be directly and primarily responsible for the funds, as well as accountable to the agency for performing the project.

In the Consortium Justification, you must provide details of any consortium agreements. This includes total costs associated with each such agreement rounded to the nearest \$1,000. You should also outline any personnel considerations, including the roles and person months, and whether the consortium involves a foreign individual or organization.

Here's an Example

The following is an example of a Consortium Justification taken from a successful R01 grant application (Tumor Necrosis Superfamily Ligands and Lymphocytes Role in Liver Regeneration. Principal Investigator: Robert A. Anders, MD):

Consortium Justification:

A consortium arrangement with the University of Chicago, a domestic institution, will be established in the estimated amount of \$108,000 per year for a total of \$538,000, direct and F&A costs.

[Professor A, MD, PhD — 9 Calendar Year person months]

[Dr. A] is a Professor of Pathology at the University of Chicago. He is an immunologist and has significant experience with the lymphotoxin system. [Dr. A's] lab cultures the hybridoma cell lines and purifies the LTbeta receptor-Ig, and agonistic LTbeta receptor antibody and performs the quality control analysis for each of these biologic agents. [Dr. A's] research interest focuses on lymph node development, autoimmunity and tumor immunology. He will serve as co-investigator and will devote [36] calendar months to the project. He will oversee and advise Dr. B.

[Assistant Professor B, MD, PhD — 9 Calendar Year person months]

[Dr. B] is a Research Associate (Assistant Professor) at the University of Chicago. He has significant experience with selective ablation of the TNF superfamily members in mice. He developed the T and B cell specific TNF and lymphotoxin deficient mice. He has also developed the hepatocyte specific lymphotoxin beta receptor deficient mice. [Dr. B's] research interest focuses on development of the peripheral immune system (spleen, Peyer's patches, limb lymph nodes) and more recently how the central immune system controls autoreactive T cells in thymus medulla. He will serve as a co-investigator on this project and will devote [36] calendar months to the project.

Additional Narrative Justification**Direct from NIH:**

If the requested budget requires any additional justification; e.g, variations in the number of modules requested, save the information in a single file and click the add attachment button to complete this entry.

What this means:

In most cases, applicants request the same number of modules each year, except for special needs like equipment. If the number of modules you request vary from year to year, this section is where you will explain why.

Use This Example

The following is an example of Additional Justification taken from a successful R01 grant application (Engineering Fibrin Polymers for Enhanced Angiogenesis. Principal Investigator: Thomas H. Barker):

Additional Narrative Justification:

Consultant fees

Funds have been requested for the consultation of [Dr. F] in years 1 through 4.

Travel

Funds have been requested to allow presentation of research results to the scientific community. Over the course of the project, we are proposing the presentation of results at 2-3 primary conferences per year.

Materials and supplies

Funds have been requested for general M&S. These funds will be used for standard laboratory supplies in support of the research objectives such as expression systems, molecular biology supplies, cell culture plastics, culture media, antibodies and reagents for detection and imaging as well as the purchase and housing of animals, surgical supplies, and histology.

Publication costs

Funds in years 2-5 have been requested to offset the cost of manuscript publication.

Equipment

In addition to the above requested funds, we are requesting additional funds for equipment. Specifically, we are requesting funds in year 1 (\$15,000) and 2 (\$10,000) for two separate and necessary upgrades to our standard inverted fluorescent microscope (Nikon TiE). These upgrades allow for 1) enhanced Z-axial imaging resolution necessary for microfluidic experiments (both fibrin polymers alone and in vitro angiogenesis assays) and 2) imaging of live cultures over time.



TIP:

In most cases, applicants request the same number of modules each year, except for special needs like equipment.

FORM A DETAILED BUDGET

Direct from NIH: The NIH Application Guides states:

The R&R Budget form includes three separate data entry screens: (1) Sections A and B; (2) Sections C through E; and (3) Sections F through K. To navigate between the various screens, use the Previous and Next buttons at the top of the form or use the scroll bar on the side of the screen. Complete the R&R Budget form following the instructions provided. You must complete a separate detailed budget for each year of support requested. The form will generate a cumulative budget for the total project period. If no funds are requested for a required field, enter “0.”

While the dollar fields allow cents to be entered, all dollar fields should be presented in whole numbers. Please round to the nearest whole number.

What this means:

If you are submitting a detailed budget, there are 11 separate sections (designated A-K) that you will have to complete. These break down as follows:

- A: Senior/Key Person
- B: Other Personnel
- C: Equipment Description
- D: Travel
- E: Participant/Trainee Support Costs
- F: Other Direct Costs
- G: Total Direct Costs (A through F)
- H: Indirect Costs
- I: Total Direct and Indirect Institutional Costs (G+H)
- J: Fee
- K: Budget Justification

The NIH application breaks these sections into three separate screens as you complete the form online:

- Screen 1: Sections A and B (Personnel)
- Screen 2: Sections C, D and E (Equipment, Travel, and Trainee Costs)
- Screen 3: Sections F through K (Other Direct and Indirect Costs and the Budget Justification)

Now, let's examine each of these sections by screen.

Start With Personnel

NIH devotes the two sections on the first screen to detailing your proposal's personnel needs.

Direct from NIH:

A. Senior/Key Person

This section should include the names of all senior/key persons at the applicant organization who are involved on the project in a particular budget year. Include all collaborating investigators, and other individuals meeting the senior/key person definition if they are from the applicant organization. Details of collaborators at other institutions will be provided in the Subaward budget for each subaward/consortium organization. Personnel listed as Other Significant Contributors who are not committing any specific measurable effort to the project should not be included in the Personnel section of the budget since no associated salary and/or fringe benefits should be requested for their contribution. Consultants designated as senior/key persons in the Senior/Key Person Profile Form can be included in Budget Section A only if they are also employees of the applicant organization. Otherwise, consultant costs should be included in Consultant Services.

What this means:

This section offers a series of data fields for each Senior/Key Person, including the following:

- First, middle and last name, along with any prefixes or suffixes
- Project role — identify each Senior/Key Person, including project directors/principal investigators, postdoctoral associates and other professionals
- Base salary — enter the annual compensation paid by the employer
- Calendar, Academic or Summer months — indicate the number of person months devoted to the project for each individual (based upon the appropriate calendar, academic or summer designations)
- Requested salary — regardless of the number of months each Senior/Key Person devotes to the project, you must identify only the salary amount you are requesting for this budget period

- Fringe benefits — enter the cash value of any applicable fringe benefits for each person. According to the NIH “the fringe benefits rate is based on your institution’s policy; the NIH does not have a pre-set limit on fringe benefits. More information on what is included as fringe benefits can be found in the Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch7.htm#Fringe_Benefits. If you have questions about what rate to use, consult your institution’s sponsored programs office.”
- Funds requested — here, note the requested salary and fringe benefits.

For Section B (Other Personnel) on this application budget screen, you will identify the number of people in each project role rather than name individuals. In fact, Section B includes the following data fields for each role:

- Number of personnel — identify the number of people you are proposing for each project role category
- Project role — the form already lists Post Doctoral Associates, Graduate Students, Undergraduate Students and Secretarial/Clerical, and you should count only those not already listed in Section A. You can list additional project roles in the additional data fields provided.
- Calendar, Academic or Summer months — indicate the number of person months devoted to the project for each project role category (based upon the calendar, academic or summer designations)
- Requested salary — show the amount of salary/wages you are requesting for each project role
- Fringe benefits — enter the cash value of any applicable fringe benefits for each project role
- Funds requested — note the requested salary and fringe benefits for each project role

Screen 2 Means Direct Expenses

NIH devotes three sections on the second screen to specifics regarding any equipment, travel and support costs associated with your proposal.

For Section C, you will separately list any equipment costing more than \$5,000. NIH defines equipment as “an item of property that has an acquisition cost of \$5,000 or more (unless the organization has established lower levels) and an expected service life of more than one year.” The agency further notes that it will allow items limited to research equipment and apparatus that you do not already have available to conduct your work. And it usually will not cover general-purpose equipment, such as personal computers, unless you use them exclusively or primarily for conducting your proposed research.

In this section, you also have to list the estimated cost of each piece of equipment, including shipping and any maintenance costs and agreements.

In Section D, you must outline your travel costs. There are separate data fields for domestic and foreign travel, which NIH breaks down as follows:

- Domestic travel — In this field, include the total funds you are requesting for travel within the United States, Canada, Mexico and U.S. possessions.
- Foreign travel — Here, you list the total funds you request for travel beyond North America and U.S. possessions.

For both types of travel, you must note in your budget justification document the purpose, destination, travel dates (if known) and number of individuals for each trip. If you do not know when the travel will take place, you must estimate the trip’s length (for example, three days).

And although the application includes Section E for participant/trainee support costs, NIH states the following:

Unless specifically stated otherwise in an announcement, NIH and other PHS agencies applicants should leave blank Section E. Note: Tuition remission for graduate students should continue to be included in Section F. Other Direct Costs when applicable.

At the same time, if you must complete this section, you will provide the total requested funding amounts related to participants and trainees involved in your project for tuition/fees/health insurance, stipends, travel and subsistence, among others.

Keep Track of Other Direct Costs

The third screen of the detailed budget form includes Sections F-K, which consist of the remaining costs associated with your proposed research.

NIH reserves Section F for Other Direct Costs. This is where you must detail the following:

- Materials and supplies — Here, you note general categories
- Publication costs
- Consultant services
- ADP/computer services
- Subawards/consortium/contractual costs
- Equipment or facility rental/user fees
- Alterations and renovations
- Other, which might include such costs as patient care and tuition remission.

For Section G (Total Direct Costs), you report the sum of the totals for Sections A-F.

In Section H, however, you will provide information regarding Indirect Costs, breaking them down by type, such as salaries and wages. Keep in mind that your institution should have this information because it usually contracts with NIH for an indirect cost rate that applies to all research conducted at the organization.

For Section I, Total Direct and Indirect Costs, you simply add the totals for Sections G and H. And Section J (Fee) is usually left blank because a fee is generally not allowed on a grant unless specifically noted in a program announcement. In that case, you should enter the requested fee.

Finally, Section K is the Budget Justification.

Direct from NIH:

Use the budget justification to provide the additional information requested in each budget category identified above and any other information the applicant wishes to submit to support the budget request. The following budget categories must be justified, where applicable: equipment, travel, participant/trainee support and other direct cost categories. Only one file may be attached. The attachment is required.

Use this section to list the names, role (e.g., PostDoc or Graduate Student), associated months, salary and fringe benefits for all Postdoctoral Associates and Graduate Students included in Budget Section B. Other Personnel.

The salaries of administrative and clerical personnel should normally be treated as F&A costs. Inclusion of such costs may be appropriate only if all of the following conditions are met:

1. Administrative or clerical services are integral to a project or activity;
2. Individuals involved can be specifically identified with the project or activity;
3. Such costs are explicitly included in the budget or have prior written approval of the Federal awarding agency; and
4. The costs are not also recovered as indirect costs

For all individuals classified as administrative/secretarial/clerical, provide a justification documenting how they meet all four conditions. NIH ICs may request additional information for these positions in order to assess allowability.

Include a justification for any significant increases or decreases from the initial year budget. Justify budgets with more than a standard escalation from the initial to the future year(s) of support. Also use this section to explain any exclusions applied to the F&A base calculation.

If the application includes a subaward/consortium budget, a separate budget justification is submitted for that budget. See Section SG.310 - R&R Subaward Budget Attachment(s) Form.

What this means:

Section K is a single narrative that you will upload to support the need for the requested funds in your application's detailed budget from Sections A-J. And you have to address each cost individually.

Because most PIs focus on their science, they frequently wait until the last minute to write the budget justification. But this is your chance to expand upon the project without taking up precious pages in the Research Strategy. In fact, the budget narrative does not count against your application page limit. Therefore, it can be your opportunity to expand upon your proposal without affecting your scientific content related to explaining your research.



STRATEGY:

The budget narrative can be your opportunity to expand upon your proposal without affecting your scientific content related to explaining your research.

This budget justification also allows you to show reviewers that you have adequately planned for your project, you have done this before, and you know what you are doing. To support this, make sure that your justification matches your overall project narrative. These two items should go hand-in-hand because you do not want a reviewer to be surprised to find an item in the budget that is not mentioned in the research strategy.

Here is a sample Section K from a successful R01 grant (Capsid-Targeting HIV-1 Antivirals. Principal Investigator: Christopher Aiken, PhD):

Budget Justification — Year 1:

Personnel

[Dr. X], Principal Investigator ([9.6] Calendar Months)

[Dr. X] will devote [80 percent] of his effort to the project. His involvement will include: overseeing the activities of the other personnel on the project, providing critical input regarding experimental design and analysis of data. [Dr. X] has extensive experience in molecular studies of HIV-1 infection, including experience in the analysis of drug resistance and antiviral mechanisms. He will communicate directly with the collaborators, and will directly participate in the presentation of results at meetings and in publications.

[Dr. Y], Research Instructor ([9.6] Calendar Months)

[Dr. Y] will devote [80 percent] effort to the project. He has performed HIV research in [Dr. X's] lab for 11 years and has extensive experience with studies of HIV-1 maturation inhibitors. He will perform the studies described in Specific Aims 3 and 5, and will report the results directly to the PI.

[Dr. Z], Research Fellow ([3.6] Calendar Months)

[Dr. Z] will contribute [30 percent] effort to the project. He joined [Dr. X's] laboratory as a postdoc in March 2009 and is currently studying the mechanism of cyclophilin A-dependent HIV-1 restriction, which will be completed in May 2010. He will perform the studies described in Specific Aim 4.

Senior Research Specialist ([9.6] Calendar Months)

[The Senior Research Specialist] has worked in [Dr. X's] lab for six years

and has extensive experience with virus propagation, assays of HIV-1 infectivity, uncoating, and host restriction as well as cell culture and protein purification. She will provide technical support to the other two scientists during the initial two years of the project, including cell culture, molecular cloning, purification of recombinant proteins, and routine infection assays. She will contribute [80 percent] of her effort to the project during Years 1 and 2, after which her effort will be reduced to [40 percent] in Year 3 and eliminated in Year 4, due to a reduced need for technical support in the later stages of the project.

Fringe Benefits

Fringe benefit calculations are derived from the current [university] guidelines. Fringe benefits are calculated at a rate of 21.9% and 26.8% for faculty and staff, respectively.

Equipment (\$10,000)

Spectrophotometer (Nanodrop: \$10,000): Funds are requested to replace our existing spectrophotometer, which is 10 years old. The instrument will be used for the quantitation of solutions containing DNA, protein, and drugs.

Supplies (\$38,000)

Cell culture (\$10,000): The proposed studies involve intensive cell culture experiments, including media, antibiotics, fetal bovine serum, and disposable plasticware.

Protein production (\$12,000): Funds are requested for supplies for expression and purification of recombinant CA proteins, including competent *E. coli* strains, IPTG for induction, buffer components (Tris, NaCl, EDTA, 2-mercaptoethanol), dialysis cassettes, columns for chromatographic purification and protein analysis, and precast gels for analysis.

Biochemicals (\$5,000): Funds are requested for specialty chemicals, including X-gal for infection assays, cyclosporine A, reverse transcriptase assay components, and supplies for p24 ELISA.

Molecular biology reagents (\$8,000): This category includes enzymes and kits for DNA purification, PCR, and molecular cloning, as well as oligonucleotide primers. The proposed work involves intensive cloning for identification of viral mutations conferring resistance.

BSL-3 supplies (\$2,400): Funds are requested to cover the cost of consumables and safety equipment for work in the BSL-3 laboratory, including protective gowns, shoe covers, gloves, bags for sterilization and waste disposal, antiseptic for decontamination of liquid waste, and eye protection.

Pipettors (\$600): Funds are requested for purchase and maintenance of micropipettors, including multichannel pipettors that are needed for the proposed studies.

Travel (\$2,500)

Funds (\$2,500) are requested for travel of both the PI and postdoc to one national meeting per year (e.g., Cold Spring Harbor Retroviruses, Keystone Symposium, and Symposium on Antiviral Drug Resistance) to present results from the project.

Other Expenses (\$6,800)

Publication Costs (\$2,000): Funds are requested to cover the costs of one publication per year during the project period.

Service contracts and certifications (\$2,400): Funds are requested to cover a portion of the service contracts for the 2 ultracentrifuges, the Li-Cor Odyssey imager, and the flow cytometer according to their anticipated use on the project. Funds are also requested to cover the costs for annual certification of 3 biosafety cabinets (2 in the BSL-3 and one in the BSL-2 laboratory).

Laboratory Analysis/Core Charges/Computer (\$2,400): Funds will cover the cost of approximately 200 sequencing reactions for identification of viral mutations. Other funds in this category include autoclaving and glasswashing services that are recovered by the Department on a fee-per-use basis. Additionally, funds requested in this category include the cost of various software upgrades and computer devices required for collection, analysis, storage, and sharing of data.

Consortium Costs (\$236,312)

[University A] (\$33,737):

The proposed studies will require analysis of HIV-1 capsid dissociation in target cells by fluorescence microscopy. This approach requires careful quantitation of CA protein levels associated with GFP-labeled cores following viral entry into target cells. For these specialized services, we have proposed to collaborate with [Dr. M]

at [University A], whose lab has pioneered this approach for the study of HIV-1 uncoating. Should funding be provided for the proposed investigations, we will enter into a consortium agreement (subcontract) with [University A]. The subcontractor's proposed budget and agreement to enter an NIH consortium is included.

[University B] (\$202,575):

The proposed studies will also require detailed structural studies of synthetic assemblies of HIV-1 CA protein and native HIV-1 cores. For these specialized services, we propose to collaborate with Drs. [N and O] in the Department of Structural Biology at [University B]. [Dr. N] is an experienced X-ray crystallographer and has recently determined a novel high-resolution structure of HIV-1 CA that will soon be reported. Her group will perform the proposed crystallographic studies. [Dr. O] is also a structural biologist specializing in electron microscopy, and her group will perform experiments involving EM (both negative stain and cryo-EM). [Dr. O's] group has recently determined the structure of cylindrical assemblies of HIV-1 CA, leading to the identification of a novel intersubunit interface that is critical to HIV-1 capsid function. Importantly, both of these investigators are members of the Center for HIV-Protein Interactions, in which [the PI] actively participates. Should funding be provided for the proposed investigations, we will enter into a consortium agreement (subcontract) with [University B]. The subcontractor's proposed budget and agreement to enter an NIH consortium is included.

Budget Justification — Year 2:

All recurring costs are incremented at a rate of 3% over year 1 to account for inflationary increases.

Budget Justification — Year 3:

The effort of the Sr. Research Specialist will be reduced to [40 percent] as we anticipate a reduced need for her technical services during the third year. All other recurring costs are incremented at a rate of 3% over year 2.

Budget Justification — Year 4:

No effort is requested in Year 4 for the Sr. Research Specialist. All other recurring costs are incremented at a rate of 3% over year 3.

On the other hand, if you are submitting a revision or supplemental application, you only need to include those budget items for which you request additional funds. And NIH says that if the initial budget period of the supplemental/revision application is less than one year, you can prorate the personnel costs and other appropriate items in your detailed budget.

NIH Has Special Instructions for Subaward/Consortiums

If your application includes a subaward or consortium agreement, NIH requires each consortium grantee organization to complete a subaward/consortium budget component, which includes a budget justification section. The agency requires this only for those organizations that perform a substantive portion of the project.

And this is necessary only when the prime grantee is submitting a detailed (R&R) budget. This is not needed if you are using a modular budget.

Remember, though, the NIH is expecting someone to be designated as the consortium lead investigator responsible for ensuring proper conduct of the project or program at that site. However, when completing the Project Role for the consortium lead investigator, the project role of “PD/PI” should only be used if the entire application is being submitted under the Multiple PI policy.

Institutions Have Deadlines, Too

Most universities and other grant-seeking organizations will not allow you to wait to submit your budget. Usually, they set a deadline of three or four weeks before the NIH submission date for you to give them your proposed budget, including all the appropriate sign-offs and consortium agreements.

In fact, many experts suggest that you address your budget as soon as you outline your grant proposal to ensure you complete it on time.

Therefore, you should check with your grants submission department to ensure you correctly understand all the institution-specific applicable deadlines for your application.



TIP:

Many experts suggest that you address your budget as soon as you outline your grant proposal to ensure you complete it on time.

CONCLUSION

Whether you request a modular or detailed budget for your R01 application, your financial planning to support your research likely should fall within the early stages so you can complete it on time — either to meet your institution’s deadlines or those for NIH.

And although modular budgets may appear easier to plan, you are limited to no more than \$250,000 per year in direct costs attributed to your proposal. Alternatively, you can request more funds with detailed budgets, but the planning process is more intensive and time-consuming.

In either case, how you explain your monetary request plays a key role in NIH’s funding decision because the justification narratives may be studied at multiple levels of the agency’s review process.

Keep in mind also that although reviewers are not supposed to include the budget as part of their overall assessment of your application, they may use it to judge your proposal’s feasibility. Therefore, you should consider it a key portion of your application. ■

Chapter 7: Submitting Your Application

Before you submit your R01 application, take time to review the finished product. Make sure your proposal works as a whole rather than a group of parts. Remember your ultimate goal is to communicate that your research deserves funding, you're the right person to conduct it, and your institution is the right place to do it.

That's why reviewing your proposal for content is important. Ensure all of the sections communicate your message adequately. Your research strategy must include strong specific aims and address your project's significance, innovation and approach. Your project summary should be a compelling synopsis of your proposed research. And your budget should be in synch with your research strategy.

Reviewing your proposal for writing quality is just as important. You may want to ask colleagues or non-experts to read your proposal and provide feedback. Or you may need to hire a professional editor.

You may also need to construct a cover letter to introduce your proposal. This is part of the National Institutes of Health's (NIH's) application upload process, and the agency encourages you to include one. If you are submitting a changed or corrected application, the cover letter is mandatory.

A new form, PHS Assignment Request Form, has been introduced by the NIH in 2016 to complement the existing cover letter. The Assignment Request Form is now used to communicate to the Division of Receipt and Referral (DRR) and to Scientific Review Officers (SROs) any specific application assignment and review requests.

In addition, make sure you have included all of your application's necessary components. Don't forget any attachments, and confirm that all attachments adhere to NIH requirements. The agency used to provide a two-day window during which applicants could fix errors, but that is no longer available. Therefore, it is extremely important to ensure all of your documents are uploaded.



TIP:

Your Research Strategy must include strong Specific Aims and address your project's Significance, Innovation and Approach.

Include All the Necessary Components

Arguably the most important step in reviewing your R01 application is making sure it is complete. There are certain components that are mandatory for all applicants, and there are parts that are required only under certain circumstances. When downloading the forms you will notice that the following all need to be filled out for the application to be deemed complete:

- SF424 (R&R) (Cover component)
- Research & Related Project/Performance Site Locations
- Research & Related Other Project Information
- Research & Related Senior/Key Person
- PHS398 Cover Page Supplement
- PHS398 Research Plan
- PHS398 Checklist
- PHS398 Modular Budget or Research & Related Budget, as appropriate
- PHS398 Inclusion Enrollment Report, as appropriate.

Optional Components

- PHS398 Cover Letter File
- Research & Related Subaward Budget Attachment(s) Form

For certain applicants, NIH requires additional components. You must take extra steps if your research involves multiple institutions or requires multiple principal investigators (PIs). The same is true if you are submitting a revision application or if you belong to a foreign institution applying for U.S. dollars.

Foreign Organizations

Applicants from foreign organizations must:

- Prepare their budgets in U.S. dollars
- Create detailed budgets for all applications (complete the research and related budget component of the SF424 application forms, not the PHS398 modular budget component)
- Omit any charge-back of customs and import fees
- Comply with the format specifications, which are based upon a standard U.S. paper size of 8.5” x 11,” within each PDF
- Facilities and administrative (F&A) costs should be 8 percent of your total direct costs, less equipment
- Comply with federal/NIH policies on human subjects, animals and biohazards
- Comply with federal/NIH biosafety and biosecurity regulations

Applications With Multiple PIs

Direct from NIH:

Multiple PD/PI Leadership Plan

For applications designating multiple PD/PIs, a leadership plan must be included. For applications designating multiple PD/PIs, all such individuals must be assigned the PD/PI role on the Senior/Key Profile form, even those at organizations other than the applicant organization. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PD/PIs and other collaborators. Do not submit a leadership plan if you are not submitting a Multiple PD/PI application. If budget allocation is planned, the distribution of resources to specific components of the project or the individual PD/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in a footnote on the Notice of Grant Award.

Attach this information as a PDF file.



REMEMBER:

The primary PI is responsible for all communications, for assembling the application materials and for coordinating progress reports.

If your project has multiple PIs, one of you must be the primary NIH contact. This person is responsible for all communication, for assembling the application materials and for coordinating progress reports. At the same time, this PI may not have other special roles or responsibilities within the project team.

The contact's information should be entered on the SF424 (R&R) cover component. All other PIs should be listed in the research and related senior/key person component as PIs. The commons (login) ID of each PI must be included in the credential field of the research and related senior/key person component. If it is not, NIH will reject the application.

You must also include a multiple PI leadership plan. The plan should describe your rationale for having more than one PI as well as the leadership team's organizational structure. You should detail communication plans, the decision-making process for scientific direction and procedures for resolving conflicts. If you have planned budget allocation, you should describe how resources will be distributed to the project's specific components or individual PIs.

Applications Involving Multiple Institutions

When multiple institutions are involved in a project, you must designate one as the prime institution. This facility must administer a subcontract to request funding for the other(s).

The prime institution should submit a detailed budget using the research and related budget component. Attach all of the other facilities' budgets separately to the research and related subaward budget attachment(s) form.

For a modular budget, the prime institution completes the PHS398 modular budget component only. The facility must then provide information concerning the consortium/subcontract budget in the budget justification. Separate budgets for each consortium/subcontract grantee are not required.

Revision Applications

A revision application is a competing supplemental application that asks for support for a significant expansion of your project's scope or research protocol. If you're submitting one, don't forget these requirements:

- A one-page introduction — “Introduction to application” section of the PHS 398 research plan — describing the supplement's nature and the impact it will have on your original proposal
- Adequate details from the original application for reviewers to evaluate the revision in the context of the original
- Budgetary changes for the remainder of the current grant's period
- A specific response to criticisms in the prior summary statement

The NIH Cautions:

Applications for revisions are not appropriate when the sole purpose is to restore awards to the full SRG-recommended level if they were administratively reduced by the funding agency. A revision application should not be submitted until after the original application has been awarded and must not extend beyond the term of the current award period.

ENSURE ALL ADDITIONS ARE ATTACHED AND COMPLY WITH GUIDELINES

Just like the application components, some additions are mandatory for all applicants, and others are required only under certain circumstances.

Conditional additions include documents that describe the use of consultants, consortium/contractual arrangements, plans for resource sharing, how you will handle select agents and how you plan to protect human subjects. Reference letters are also required conditionally.

Conversely, all applicants must include additions describing facilities and other resources, as well as a bibliography. If your research requires documents such as informed consent forms or surveys, you must include them in an appendix.



TIP:

Do not include essential information in the appendix in an attempt to circumvent the research plan's page limitations.

Appendix Materials

The appendix should only contain supportive or supplemental information. Do not include essential information in the appendix in an attempt to circumvent the research plan's page limitations.

You are allowed a maximum of 10 PDF attachments. If you require more than 10, you can combine the information into attachment No. 10.

New, resubmission, renewal and revision applications may include the following materials in the appendix:

- 1) Although publications are not allowed as appendix materials in most cases, applicants may sometimes submit up to three of the following types of publications:
 - a. Manuscripts and/or abstracts accepted for publication but not yet published.
 - b. Manuscripts and/or abstracts that have been published, but a free, online, publicly available journal link is not available.
 - c. Patents directly relevant to the project.

Do not include unpublished theses or abstracts/manuscripts submitted (but not yet accepted) for publication.

- 2) Clinical protocols, informed consent documents and data collection instruments such as surveys and questionnaires

- 3) For materials that cannot be submitted electronically or materials that cannot be converted to PDF format (e.g., medical devices, prototypes, DVDs, CDs), contact the scientific review officer (SRO) for instructions. Be as concise as possible, and submit only information essential for the application's review.

Do not include these items in the appendix:

- 1) Photographs or color images of gels, micrographs, etc. You must include these images in the research strategy PDF. However, images embedded in publications are allowed.
- 2) Publications that are publicly accessible. Include the URL or PubMed submission identification numbers in the bibliography, the progress report publication list section or the biographical sketch section.

Bibliography

There is no specific format to which your bibliography must adhere. Just ensure that it includes all references cited in the research plan, and references are arranged in the same sequence as they appear in the document. Each listing must include the names of all authors, the article and journal title or the book title, the volume number, page numbers and year of publication.

Only include bibliographic citations. Follow scholarly practices in providing citations for source materials relied upon when preparing any application section.

The location of this information is slightly different in the SF424 R&R and the PHS398. Be sure to read the application instructions carefully for the application you are using.

Facilities and Other Resources

Make sure you have identified the facilities you will use (laboratory, animal, computer, office, clinical and other). If appropriate, indicate their capacities, pertinent capabilities, relative proximity and availability to the project. Describe only those resources directly applicable to your work.

Consortium/Contractual Arrangements

Explain the programmatic, fiscal and administrative arrangements between the applicant organization and the consortium organization(s).

Consultants

Attach letters from all consultants that confirm their project roles. The letters should include the charge for consulting services.

Protecting Human Subjects From Risk

NIH will not distribute awards unless human protection assurances are on file with the Office for Human Research Protections (OHRP).

Resource-Sharing Plan(s), Including Data-Sharing Plans

You must share final research data for applications that seek \$500,000 or more in direct costs in any year of the grant. The same is true for some program announcements and all genome-wide association studies. Describe your resource-sharing plan — or justify its absence — in a brief paragraph in your research plan.

Select Agents

Have you identified any select agents to be used in the proposed research? These are hazardous biological agents and toxins the U.S. Department of Health and Human Services (HHS) or U.S. Department of Agriculture identify as able to pose a severe threat to public health and safety, animal and plant health, or animal and plant products.

If your proposed research involves using select agents, your application has to detail how you'll use them. But how can you best convey to reviewers that you've thoroughly considered safely handling these dangerous substances? Following these recommendations can help:

- Resist the temptation to merely “touch up” the boilerplate language your university provides. True, customary information from your institution gets you started. But reviewers are looking for more than that. They want your plan's specific details.

- Double-check information security. Regulators want to know you'll protect against accidental release of agents that can harm people, animals and plants. They also recognize that some of the biohazards have the potential for bio-terrorism. So outline your information security measures.
- Explain your backup plans. Reviewers know what can go wrong and want to know that you've considered it. A short description addressing common problems goes a long way toward establishing your credibility.
- Focus on existing facilities, equipment and experience. Lacking any of these will hurt you. NIH doesn't want to pay for your learning curve or expensive facilities.

Reference Letters

Note there are two types of reference letters:

- 1) A letter of recommendation is from a faculty member or other person qualified to evaluate your proposal's merit and your qualifications.
- 2) A letter of support is typically from an outside individual whose assistance you will need to ensure your project's success. This letter is meant to establish your credibility, convince the review board your project is feasible and detail the type of support promised.

You can only include reference letters if they are specifically requested in the funding opportunity announcement (FOA) or application guide. You can submit them as soon as the FOA opens, even prior to sending in your application.

Reference letters are linked by FOA number and your Commons user ID. If you don't provide these values or enter them incorrectly, the letter never connects to the application. Orphaned letters are deleted from eRA Commons after six months.

If you are submitting a changed or corrected application to address eRA-identified errors/warnings, the reference letters will automatically move to the most recent application submission for a specific opportunity deadline. Reference letters that come in electronically must be uploaded electronically via eRA Commons.

If your original application was rejected, and you decide to resubmit as an A1 application, you cannot use the same reference letter(s). You must submit new ones for each opportunity.

Unless stated, the aforementioned attachments do not influence your application's rating (priority score). Your reviewers will comment on the attachments' adequacy, however. Any concerns they have may negatively affect and postpone an award.

Frequently Asked Questions About Attachments

Q. What type of attachments does NIH accept?

A. PDFs. But if an attachment can't be submitted electronically, the agency will accept a hard copy.

Q. Who is responsible for generating the PDF documents?

A. The applicant or their institution's grant office.

Q. How does an applicant submit appendix material that he cannot send electronically?

A. Mail "hard" appendix materials, such as a video or heart valve, to the SRO and then the reviewers.

Q. How does NIH accommodate appendix material?

A. There is an attachment upload available. You can include up to 10 separate PDF attachments. The appendix attachment upload feature is in the PHS 398 research plan component.

Q. How does NIH accommodate supplemental/additional/correction material submitted after the application?

A. Supplemental/additional/correction material must be submitted through, and at the discretion of, the assigned SRO. Some FOAs prohibit the submission of supplemental/additional/correction materials.

Q. How does the NIH handle administrative supplements?

A. Individual institutes and centers handle them.

CREATE A COVER LETTER

Although it's not always required, NIH strongly recommends that you submit a cover letter with your grant application. Keep in mind the agency likely will use the letter to help assign your proposal to the right study section.

Direct from NIH:

Attach the cover letter, addressed to the Division of Receipt and Referral, in accordance with the announcement and/or the agency specific instructions.

Applicants are encouraged to include a cover letter with the competing application. Please attach the cover letter in the correct location, specifically verify that the cover letter has not been uploaded to the pre-application field which is directly above the cover letter field. This will ensure the attachment is kept separate from the assembled application in Commons and only made available to appropriate staff.

A cover letter should not be included with post-award submissions such as administrative supplements, change of grantee institution, or successor-in-interest. The cover letter is only for internal use and will not be shared with peer reviewers. The letter should contain any of the following information that applies to the application:

1. Application title.
2. Funding Opportunity (PA or RFA) title of the NIH initiative
3. For late applications (see Late Application policy in <http://grants.nih.gov/grants/funding/submissionpolicies.htm>) include specific information about the timing and nature of the cause of the delay.
4. When submitting a Changed/Corrected Application after the due date, a cover letter is required explaining the reason for late submission of the Changed/Corrected Application. If you already submitted a cover letter with a previous submission and are now submitting a late Changed/Corrected Application, you must include all previous cover letter text in the revised cover letter attachment. The system does not retain any previously submitted cover letters; therefore, you must repeat all information previously submitted in the cover letter as well as any additional information.
5. Explanation of any subaward budget components that are not active for all periods of the proposed grant Section G.240 - Senior/Key Person Profile (Expanded) Form.



REMEMBER:

When submitting a video as part of your proposal you must state this within your cover letter.

6. Statement that you have attached any required agency approval documentation for the type of application submitted. This may include approval for applications \$500,000 or more, approval for Conference Grant or Cooperative Agreement (R13 or U13), etc. It is recommended that you include the official communication from an NIH official as part of your cover letter.
7. When intending to submit a video as part of the application, the cover letter must include information about the intent to submit it; if this is not done, a video will not be accepted. See NOT-OD-12-141 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-141.html>) for additional information.
8. Include a statement in the cover letter if the proposed studies will generate large-scale human or non-human genomic data as detailed in the NIH Genomic Data Sharing Policy (NOT-OD-14-11: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-111.html> and NOT-OD-15-027: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-027.html>.)

The cover letter is only for internal use and will not be shared with peer reviewers. The letter is required for any of the following applications:

- Resubmissions
- Any applications which require NIH approval before submission
- Applications including genome-wide studies
- Corrected applications
- Late applications
- Continuous submissions
- If you are submitting a video component with your proposal
- A cover letter is recommended but not required for the following purposes:
 - State RFAs or Pas when responding to an initiative
 - Proposals that include human subjects, select agents, genome-wide studies or study data, or other special requirements
 - Any subaward that will be active for only a portion of the grant's years

Be sure not to confuse the cover letter file with the PHS 398 Cover Page Supplement form. The Cover Page Supplement form is required for all proposals and collects information on the inclusion of human subjects, vertebrate animals, program income, human embryonic stem cells, inventions and patents, and change of investigator/change of institution.

COMPLETE AN ASSIGNMENT REQUEST FORM

Prior to 2016, cover letters were also used to convey any specific requests for peer review assignment. Now this information is submitted by utilizing the new Assignment Request Form. Although this form is optional, experts suggest to submit this form as it will help the Division of Receipt and Referral and Scientific Review Officers assign your proposal to the correct Institutes/Centers and SRGs. Additionally, this form is also used to advise of any potential conflict of interests during the review process.

The Division of Receipt and Referral (DRR), Center for Scientific Review (CSR) is responsible for assigning applications to NIH institutes/centers (ICs) and other PHS agencies for funding consideration. DRR also assigns application to NIH scientific review groups (SRGs) and special emphasis panels (SEPs).

This form is optional and may be omitted from your application submission if you do not wish to make any specific assignment or review requests. There is no requirement that all fields in the form are completed; you have the flexibility to enter a single request or provide extensive information using this form.



STRATEGY:

Although you should never request individual reviewers by name, you can ask for those with a specific area of expertise.

The form includes the following optional fields:

1. Awarding Component Assignment Request: Request up to three Institutes/Centers using their appropriate abbreviations (e.g., NCI, NIAID, etc.) in order of preference
 - Assign to Awarding Component
 - Do Not Assign to Awarding Component
2. Study Section Assignment Request: Using the appropriate abbreviations, request up to three SRGs or SEPs in order of preference. (For a list of abbreviations visit: http://grants.nih.gov/grants/phs_assignment_information.htm#StudySection)
 - Assign to Study Section
 - Do Not Assign to Study Section
3. List individuals who should not review your application and why: Using a maximum of 1000 characters provide the name, organizational affiliation, and explanation of any conflict of interest.
4. Identify expertise needed to review your application: List up to five general or specific expertise which is need to review your application.

PHS Assignment Request Form

View Burden Statement

PHS Assignment Request Form

OMB Number: 0925-0001
 Expiration Date: 10/31/2018

Funding Opportunity Number:

Funding Opportunity Title:

Awarding Component Assignment Request (optional)

If you have a preference for an Awarding Component (e.g., NIH Institute/Center) assignment, please use the link below to identify the most appropriate assignment then enter the short abbreviation (e.g., NCI for National Cancer Institute) in "Assign to/Do Not Assign To Awarding Component" sections below. Your first choice should be in column 1. All requests will be considered, however, locus of review is predetermined for some applications and assignment requests cannot always be honored.

Information about Awarding Components can be found here: https://grants.nih.gov/grants/phs_assignment_information.htm#Awarding Components

	1	2	3
Assign to Awarding Component:	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>
Do Not Assign to Awarding Component:	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>

Study Section Assignment Request (optional)

If you have a preference for a study section assignment, please use the link below to identify the most appropriate study section then enter the short abbreviation for that study section in "Assign to/Do not Assign to Study Section" sections below. Your first choice should be in column 1. All requests will be considered, however, locus of review is predetermined for some applications and assignment requests cannot always be honored.

For example, you would enter "CAMP" if you wish to request assignment to the Cancer Molecular Pathobiology study section or enter "ZRG1 HDM-R" if you wish to request assignment to the Healthcare Delivery and Methodologies SBIR/STTR panel for informatics. Be careful to accurately capture all formatting (e.g., spaces, hyphens) when you type in the request.

Information about Study Sections can be found here: https://grants.nih.gov/grants/phs_assignment_information.htm#Study Section

	1	2	3
Assign to Study Section: <i>Only 20 characters allowed</i>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>
Do Not Assign to Study Section: <i>Only 20 characters allowed</i>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>	<input style="width: 80%; height: 15px; border: 1px solid #ccc;" type="text"/>

Making Peer Review Suggestions

There are tips you should keep in mind when making peer review suggestions in your Assignment Request Form. First, never request individual reviewers by name. But you can ask for reviewers with a specific area of expertise.

Analysis has shown that requests for expertise (as long as reviewers go unnamed) are a valuable source of information when NIH selects peer reviewers. When you make this suggestion, you can include any of the following:

- Suggestions of study sections or funding agencies best suited to a proposal. Include advice you received from a program director or SRO about a study section or institute.
- For multidisciplinary applications, highlight the application’s main disciplinary/methodological thrust.
- Include a list of research disciplines critical to understanding your application.

It's also perfectly acceptable for you to learn about peer reviewers by viewing SRG rosters at <https://public.era.nih.gov/pubroster/>. But you should never communicate directly with a review group member about an application, either before or after review. Peer reviewers must report to SROs any direct or attempted contact by applicants.

Communicating Conflict of Interest

Include information regarding a conflict of interest, or a potential conflict, in your Assignment Request Form. For example, say you request a specific study section to review your application. But the roster indicates that a direct competitor, a former mentor or a former student is a member of that study section. To request the exclusion of a reviewer:

- List the individual's name and organization affiliation.
- Provide a sufficient description of why the person should not be involved in reviewing your application.

REVIEW YOUR PROPOSAL FOR CONTENT



REMEMBER:

Your Abstract is the first component reviewers read, and it may actually be the **only** part they read, setting the tone for your entire application.



STRATEGY:

Tell reviewers why testing your hypothesis is worth NIH's money, why you are the person to do it and how your institution can give you the support you'll need to get it done.

So you've assembled the necessary components, included the required attachments and written a comprehensive cover letter. Now, it's time to review your proposal's content. Examine the most important sections closely. Ensure your abstract is a compelling, detailed summary of your research. Make certain your budget is in synch with your research strategy. Evaluate your specific aims, and assess how you've described your project's significance, innovation and approach.

Project Summary/Abstract

Your project summary should succinctly describe every major aspect of your project. But it should not exceed 30 lines. If an abstract is too long, NIH will flag it as an error.

Your project summary must include these parts.

- A brief background of the project
- Specific aims, objectives or hypotheses
- The significance of your research and its relevance to public health
- Your project's unique features and innovation
- The methodology (action steps) to be used
- Expected results
- Description of how your results will affect other research areas

Remember that your abstract is the first component reviewers read, and it may actually be the *only* part they read. It sets the tone for your application and should be a good predictor of the proposal that follows. It also becomes the primary identifier for your project and may be used for public dissemination in the future.

Make sure your project summary:

- Follows the proposal's logic and order
- Is composed of short, direct sentences
- Clearly details your hypothesis
- Has been proofed and edited rigorously

Don't:

- Just cut and paste sections from your proposal
- Forget to describe the problem
- Include too much obvious background information
- Use jargon, acronyms, symbols and abbreviations
- Include figures, tables or references

Budget

Your budget tells reviewers more than just how much money you want. Make sure it accurately reflects the resources you will need and the expenses you expect to incur. Were you realistic in your request? Both padding and deliberately under-budgeting reflect naiveté, and reviewers will notice.

Special forms are provided for the budget and justification. NIH recommends the budget and justification cover personnel, consultants, equipment, supplies, travel and other expenses (for example, animal maintenance). Make sure you provided brief descriptions of duties for all budgeted positions, with the number of person-months requested each year and any anticipated fluctuations. Try to eliminate as many “to be named” personnel designations as you can. They’re often deleted by reviewers.

If you use a modular budget, you do not need to detail supplies, equipment and travel costs. But for non-modular budgets, make sure you justified all equipment purchases. Details are important, especially for non-project specific equipment, such as a fax machine and computers.

Also, be sure to check indirect costs. Some institutions have on-campus and off-campus rates. If applicable, also provide documentation of institutional rates for animal maintenance and acquisition. Exceptionally large numbers of animals will need detailed justification.

If you have any questions or concerns, review the budget with your institution’s budget department. Requirements and terminology tend to differ from agency to agency and award to award. For example, a PI may only have experience measuring effort in percentages. Therefore, the NIH approach of measuring effort in “person-months” may prove confusing.



REMEMBER:

Some grant programs are subject to legislatively imposed salary limitations, and any salary limit adjustments are made at the time of award. Compensation includes salary or wages, fringe benefits and tuition remission.

You should also verify cost estimates with internal and external experts. This can help you accurately estimate and plan project tasks (for instance, international travel considerations, conference venues and equipment quotes).

Reviewing your budget and the project description simultaneously can be helpful as well. This ensures your project scope does not exceed the agency's maximum budget request.

Research Strategy

The Research Strategy is organized into three sections: significance, innovation and approach. Reviewers' assessment of these sections will largely determine whether your application is recommended for funding.

Ensure all sections are internally consistent and dovetail each other. Did you use a numbering system and make sections easy to find? Did you lead the reviewers through your research plan? Make sure your research strategy section answers these questions:

- What do you intend to do?
- Why is it worth doing? What is the research's significance? How is it innovative?
- What have other researchers done in this field? Use appropriate references. What will your work add to the field of knowledge?
- What have you (and your collaborators) done to establish your project's feasibility?
- How will you accomplish the research? Who will do it, where will they do it, and when?
- Did you address the rigor and transparency detailing the scientific premise, emphasizing how your methods will achieve unbiased results, relevant biological variables, and authentication of key biological and/or chemical resources?

Specific Aims

For the section on Specific Aims, make sure you include a brief narrative describing your project's long-term goals or objectives and your hypothesis. Then follow with your list of aims.

You should only include three or four. That's because one or two aims likely will not have a broad enough scope to provide any real impact on a field. But more than four aims will be difficult to fully develop.

In crafting an effective and convincing Specific Aim, consider the aim's characteristics and its relationship to the others. It is best if one aim is not strictly dependent on the success of the others. If your aims are sequential, tell the reviewers what you intend to do if you get an unexpected result in the first one — that is, why the whole project would not collapse.

Significance

Ensure you cover the state of existing knowledge, including both strengths and weaknesses, literature citations and highlights of relevant data. You should also include the proposed research's rationale, any knowledge gaps the project will fill, and the potential contribution your research will make to science and public health.

Clearly state what is significant about your research. You want to point out what you are going to achieve that's different from other research projects.

Cautionary example: “HIV is a retrovirus that has caused a worldwide epidemic of AIDS. More than 33 million people are affected with HIV globally. As a retrovirus, HIV integrates into the host chromosome. Anti-virals are not without complications; resistance to current drugs occurs frequently.”

This is basic information, and it's correct. But it doesn't indicate what the researchers plan to do or what is significant about the proposal.

Better: Include a clear statement that follows the above, such as, “This proposal is designed to discover more about anti-viral drugs and see what can be done to reduce resistance.”

Innovation

This section should explain why your concepts and methods are novel. Focus on innovation in study design and outcomes. And summarize findings to be presented as preliminary data in the Approach section.

Keep in mind that a reviewer's response to scientific innovation will vary. This will depend upon how extensively he has read in his own field, how broadly his knowledge extends to other fields, and how much novelty and risk he is willing to tolerate.

Reviewers tend to be on the conservative side when it comes to awarding grants. They hesitate to support work at the earlier, potentially more innovative stages. Science that is truly revolutionary threatens the existing order, putting at risk the significance and validity of current dogma.

Additionally, reviewers often believe a grant must have enough preliminary data to eliminate significant uncertainty about the central hypothesis but not so much that further investment won't yield additional high-impact papers.

Approach

This section should include the following:

- Your preliminary studies, data and experience relevant to the project design
- A succinct description of the experimental design and methods with enough detail to assure reviewers that the necessary elements of rigor are addressed.
- A description of methods and analyses that will accomplish the project's specific aims
- A discussion of potential difficulties and limitations and how these will be overcome
- Expected results and alternative approaches that will be used if unexpected results occur
- A projected sequence or timetable (work plan)
- If the project is in early stages, a description of any strategy to establish feasibility and the management of any high-risk aspects
- A detailed discussion of the way results will be collected, analyzed and interpreted
- A description of new methodology and why it represents an improvement over the existing ones



REMEMBER:

Reviewers tend to focus on the Approach section because they can assess logical and technical flaws there more objectively than in other sections.

Reviewers tend to focus on the Approach section because they can assess logical and technical flaws there more objectively than in other sections.

The NIH's Office of Extramural Research previously looked at the five reviewing criteria (Approach, Significance, Innovation, Investigator and Environment) and how well scores for each factor correlate with an application's

Overall Impact score. The score for Approach turned out to be the best predictor of Overall Impact, correlating to Overall Impact in 82 percent of funded applications.

The Approach section is also where many new PIs make one or more standard errors that are relatively easy to identify:

- The applicant is “overly ambitious”
- One or more aims are “unfocused” or “underdeveloped”
- An aim is just a “fishing expedition” for a missing gene or interactions
- There’s too little description of results analysis
- Over-reliance on a preferred hypothesis
- An aim is just too “risky”

Anticipating these critiques when reviewing your proposal is one of the best defenses you have. Knowing that the Approach score provides the strongest correlation to your Overall Impact rating shows this section is where you should devote most of your reviewing time.

After you’ve reread your research plan, ask yourself these questions:

- Did you include preliminary data or a progress report?
- Did you avoid excessive experimental detail by referring to publications that describe the methods to be employed? Publications cited should be by you, if possible.
- Did you, if relevant, explain why one approach or method will be used over others? This shows you did not simply overlook the alternatives.
- If you’re employing a complex technology for the first time, did you take extra care to demonstrate familiarity with it?
- Did you explain how data will be collected, analyzed and interpreted?
- Did you develop alternative strategies for potential problems?
- Did you include any resource-sharing plans?
- Did you document proposed collaborations and offers of materials or reagents of restricted availability with letters?
- Did you point out any procedures, situations or materials that may be hazardous to personnel and describe precautions to be exercised?

REVIEW YOUR PROPOSAL FOR WRITING QUALITY

Once you've assessed your application's content, look at the quality of your writing. Does your proposal clearly communicate the message you want to convey? Is it concise and to-the-point? Are there grammatical, spelling or punctuation errors?

Take these NIH-recommended editing steps:

- Allow enough time so you can put the completed application aside and later edit it from a fresh vantage point. You may only need to break for a few hours, or you may need a few days. When you go back to your proposal, try reading it aloud.
- Allow at least a few weeks for an internal review by collaborators, colleagues and mentors. Make revisions/edits from that review. If possible, have experts in your field and those who are less familiar with your science provide feedback. The application should be easily understood by all.
- If more than one investigator has contributed to the application, the writing may not be cohesive. Employ one overall editor to ensure the sections work together.
- Have zero tolerance for typographical errors, misspellings, grammatical mistakes or sloppy formatting. A disorganized application may convince reviewers you will conduct your research in the same manner.
- Perform a final proofread of the entire grant application.

Writing Examples

Unclear writing: “It is important to realize that, due to the highly ruminant nature of giraffes, there exists an opportunity for deleterious or unpredicted results. Some results may include: a) generation of unreasonable and/or potentially unviable offspring, b) depletion of the natural environment of foliage and c) desecration/obliteration of migrational pathways.”

An improvement: “Highly ruminant giraffes may produce harmful or unexpected results, such as generation of unreasonable or otherwise unviable offspring, depletion

of foliage, and desecration or obliteration of migrational pathways.”

The second example is 28 words, versus the initial 49. But nothing significant from the first version is missing from the second. We substituted “harmful” for “deleterious;” that’s two easy-to-understand syllables for five fancy ones. The giraffes, the subjects of the research, are in their rightful place as subjects of the sentence. We took out an unnecessary statement — “It is important to realize that” — but there’s still more trimming to do.

Further improvement: “Ruminant giraffes may generate unreasonable or otherwise unviable offspring, deplete foliage, and desecrate or obliterate migrational pathways.”

The final example is a mere 17 words. The scientific sense is still there, with a 65 percent saving in word count over the original version. In the course of a 15-page proposal narrative, that’s like giving yourself 10 extra pages to explain your research. Now, look back at the first version of this paragraph and ask yourself what job the extra 32 words were doing. The answer is, nothing useful, and a lot that hurts the proposal’s chances.

Hiring a Professional Editor

You may want to hire an editor to ensure your application is error-free. A professional can ensure your proposal says what you really mean. Editors-for-hire can provide these services:

- Copy editing or line editing, which includes correcting style; clarifying expression; making suggestions for structure; and ensuring proper use of grammar, diction and syntax. Professional editors can improve these fairly quickly if there are no underlying problems with the science.
- Content review. What appears to be a writing problem may actually be a content problem. These boil down to two kinds:
 - 1) You’re not sure what you’re really trying to say.
 - 2) There’s a problem with the concept itself. You should be able to say: “This study was conducted this way and produced these results, with these caveats and limits.”

Example: “There is evidence of the efficacy of cognitive-behavioral therapy in reducing chronic pain in some subsets of the population.” This naturally leads the reader to ask a series of questions: Which subset? How were these isolated? What kinds of testing uncovered these results? How much was learned, and how much remains unknown? The structure of the improved paper can now be visualized.

Consider hiring an editor if:

- You don't have enough time to polish or hone your application. Or you've lost focus and will lose a lot of time trying to find it.
- You're not a very good writer. A professional grant writer can offer you form compositional structures that will allow readers to easily understand what you're saying.
- Many researchers are involved. The application can easily lose focus if the investigators can't agree. Sometimes a third party can step in and find ways to create a single vision.
- English isn't your first language.

11 SIMPLE MISTAKES THAT CAN DERAIL YOUR GRANT APPLICATION

Often, the simplest, most basic errors can hurt grant applicants the most. Here are 11 of them:

- 1) Failing to allocate enough time to write. Typically, you can assume you will need 120 hours to write, review and revise an NIH application for a three- to five-year grant. A smaller, non-governmental grant can take three or four months to complete. Bottom line: Overestimate the time you think you'll need, and plan all your timelines accordingly.
- 2) Skipping the instructions. Do not bend, modify or get creative with them. Follow rules regarding font, font size, margins and word count. Pay attention to details on allowable budget expenses. When in doubt, contact the program officer.
- 3) Poor writing. Don't assume the reader understands your jargon and can follow the compelling rationale or breach the gaps in your logic. Lead the reviewer to logical and natural conclusions. Keep abbreviations, strange acronyms and jargon to a minimum.
- 4) Failing to edit. As mentioned previously, you should edit your proposal yourself and ask others for feedback.
- 5) Inadvertent plagiarism. The NIH runs all grant proposals through plagiarism programs. Before submitting yours, do the same. Programs include iThenticate, Plagiarism Detector and Copyscape. You can even enter sections of your proposal into a search engine to be sure you haven't inadvertently copied from someone else's research.
- 6) Forgetting the responsible conduct of research plan. You are required to have one for all students (graduate or undergraduate) or postdoctoral researchers who receive a salary from your grant. This ensures appropriate training and oversight. Discuss your plan with your compliance office to be sure you have the right measures in place.
- 7) The reviewers did not find your central scientific question interesting. Arguably, the single most common reason for a grant receiving a low score is reviewers'



TIP:

Don't assume the reader understands your jargon and can follow the compelling rationale or breach the gaps in your logic.

perception that your central scientific question lacks significance. Reviewer uninterest in your question could stem from your failure to communicate its significance clearly, an overly narrow focus, or a lack of novelty and originality that suggests you are addressing a problem already solved.

One way to test your proposal's significance is to provide a non-expert colleague with a three-sentence description. If he or she can appreciate why you are doing the work, then you are on the right track.

- 8) The preliminary data are weak and call into question your proposal's feasibility. Or there is an overly large gap between your hypothesis and your preliminary data.
- 9) The overall success of your project depends upon the outcome of a key experiment, which you have not performed. There is a natural tendency to organize experiments in a linear and sequential fashion. For a research grant, however, this strategy can be risky. If the succeeding aims all depend on a positive outcome of Aim One (which is yet unproven), your whole project depends on that first experiment's success.
- 10) The project's scope is too ambitious, with multiple hypotheses or rationales that pull the grant in disparate directions. This is called "spaghetti syndrome," in which every good hypothesis, experiment or reagent in the PI's pantry is thrown at the problem. This approach rests on the assumption that reviewers will find at least a few good ideas stuck on the proverbial wall, and this will raise their enthusiasm. In reality, this approach diminishes enthusiasm. It suggests a PI is unable to prioritize among the project's various facets, which can lead to an inefficient deployment of people and resources.
- 11) The PI or research team lacks the experience to carry out the proposed work. For first-time and early investigators, reviewers will assess training and accomplishments during the postdoctoral years. For more senior investigators, reviewers will look at past career experience and productivity. If a particular approach is unproven with respect to your lab, the most reliable strategies are:
 - a) Identifying and soliciting an outside collaborator with a published track record in the method
 - b) Devoting existing lab efforts to generate the preliminary data and remove doubts about your ability.

MAKE THESE FINAL CHECKS

Below is a list of some of the more common errors made by applicants, based on historical information accumulated by the NIH :

- Does the data universal numbering system number on the SF424 (R&R) cover form match the system for grants.gov and commons registration?
- Did you include the eRA commons ID in the credential field of the R&R senior/key person profile form for all PIs? This is critical to NIH's ability to post errors, warnings and the assembled application image in eRA commons.
- Did you include the organization name for all senior/key people listed on the R&R senior/key person profile form?
- Did you follow the page limits specified in the FOA and application guide?
- Did you use an allowable font type and size?
- Did you provide the correct type of submission, federal identifier and type of application information on the SF424 (R&R) cover form?

On initial submission, the type should be set to “application.” For subsequent submissions, it should be set to “changed/corrected.”

Changed/corrected applications sent in before the due date do not require a cover letter. Any application submitted after the due date must include one. For electronic submissions, the cover letter is a PDF attachment to the PHS 398 cover letter file component in the optional documents section.

There are nine application types you can use to identify the stages in a grant's life cycle. The type defines the procedures and specifies the documents required to process the award. You can only choose one.

- 1) New: A request for support of a project that has not been funded
- 2) Competing continuation: An appeal for an additional support period based on a previously funded project

**TIP:**

NIH uses the HHS logo within the application guide to flag agency-specific instructions and clarifications for fields on federal-wide forms. Pay special attention to the HHS logo, or you may miss key NIH requirements.

- 3) Supplement: A solicitation for additional funds, either for the current operating year or for any future year, to cover increased costs (noncompeting) or to expand the scope of work (competing)
- 4) Extension: A request for additional time and/or funds beyond those previously awarded. These are typically limited to certain mechanisms, including Merit (R37), Developmental/Exploratory (R21/R33) and Fast-Track Small Business Grants SBIR/STTR (R42/R44). These grants do not compete for available funds.
- 5) Noncompeting grant progress report: An appeal to pay the next budget increment of a current award. This does not compete for available funds.
- 6) Change of institute or division: A request for NIH's acceptance of a change in business structure, such as successor-in-interest, name change or merger
- 7) Change of grantee or training institution: An appeal for support of a funded project to be transferred from one grantee or training institution to another
- 8) Change of institute or center: A noncompeting continuation to be transferred from one institute to another
- 9) Change of institute or center: A competing continuation that has been transferred from one institute to another

SUBMITTING THE APPLICATION

Typically, the authorized organization representative (AOR) will submit all application materials. A PI can submit materials with the AOR's approval, but NIH won't accept materials that have not been approved.

To submit your proposal, go to the grants.gov login page and enter your username and password. Once you are logged in, the application package will be automatically uploaded to the website. A confirmation screen appears once the upload is complete, and a grants.gov tracking number is provided. Keep this number for your records.

If everything is acceptable, no further action is necessary. The application will automatically move forward to the Division of Receipt and Referral in the Center for Scientific Review for processing.

On the other hand, if some part of the proposal was lost or did not transfer correctly during the submission process, the AOR can reject it and submit a changed/corrected application. In these cases, you should contact the eRA help desk to ensure the issues are addressed and corrected. Once you've rejected the proposal, follow the instructions for correcting errors, including the requirement for cover letters on late applications.

Also use the reject feature if you determine that warnings are applicable to your proposal and must be addressed now. Remember, warnings do not stop the application process. If a submission results in warnings (but no errors), it will automatically move forward after two weekdays. Work with your AOR/signing official to determine when the reject feature is appropriate.

You may find you need to submit supplementary or corrective material after your due date — for example, revised budget pages, updated biographical sketches, letters of recommendation or publications that have been accepted but not published. Acceptance of those materials is at the discretion of the NIH SRO. Be sure to send any additional documents as PDF attachments to emails.

You must submit additional materials to the SRO with the consent of your AOR, and the AOR should be copied on correspondence to the SRO.

SHOULD YOU WITHDRAW THE APPLICATION?

Procedure

At any time, a PI may withdraw an application after submitting it if he or she decides not to pursue funding, or the application has a problem that needs to be addressed for a future receipt date.

This SOP addresses withdrawing an application after the Division of Receipt and Referral (DRR) (http://grants.nih.gov/grants/receipt_referral.htm) in NIH's Center for Scientific Review (CSR) receives it. For information on withdrawing an electronic application in response to validation issues, see Assess Your Application After You Submit (<https://www.niaid.nih.gov/researchfunding/grant/strategy/pages/4assess.aspx>) in Strategy for a Successful Submission (<https://www.niaid.nih.gov/researchfunding/grant/strategy/pages/4stratsub.aspx>) in the Strategy for NIH Funding (<https://www.niaid.nih.gov/researchfunding/grant/strategy/pages/default.aspx>).

PIs should consider the following before withdrawing an application:

- Institutional business officials must sign off on all withdrawal requests.
- Applications withdrawn before initial peer review will not count as one of the allowed submissions.
- Applications withdrawn after initial peer review will count as one of the allowed submissions.
 - Note: when PIs withdraw their application after peer review but before NIH releases their summary statements, they do not receive a summary statement and lose their opportunity to resubmit.

Multiple active applications. To send a resubmission, an applicant does not need to withdraw the previous one. The eRA Commons (<https://commons.era.nih.gov/commons/>) allows multiple active applications (MAA) in the system at the same time.

- Applicants may submit an amended version of an application before the previous application has made its way completely through the Council and funding decision processes.
- All active versions of the application in the Commons show an “MAA” flag and are considered part of a cluster.
- If any version of an application in a cluster is awarded, all other applications within the cluster will be automatically withdrawn.

Multiple PI applications. Only the contact PI may request withdrawal of an application.

Principal Investigators

- Request to withdraw your application by sending a letter to DRR.
 - Include your name, application title, and funding opportunity announcement number.
 - Make sure your institutional business official signs the request.
 - Send the letter as an email attachment to csrdr@mail.nih.gov. This is the preferred method.
 - Send faxed requests to 301-480-1987. Faxes take longer to process.
- Alternatively, ask your program officer to withdraw your application. Send your program officer a letter signed by you and your institutional business official.
 - Program officers: forward the letter to your division coordinators and have them initiate an ACR for withdrawal.

CONCLUSION

Congratulations on your submission. You made the application deadline and there were no errors that could sidetrack your proposal's advancement towards review. Since you planned and executed the writing of your proposal well in advance, and are comfortable and confident on its content, there should be no reason for you to withdraw your application. ■

Chapter 8: The NIH Application Review Process

This chapter outlines the National Institutes of Health's (NIH) review process. It describes how the Center for Scientific Review assesses applications and assigns them to review groups. It also explains how your application moves from an integrated review group (IRG) to a scientific review group (SRG) to an institute or center's advisory board or council.

You'll learn the four steps of the initial peer review process and how an SRG (otherwise known as a study section) rates your application. We describe how five criteria — Significance, Innovation, Approach, Investigators and Environment — are used to score your proposal. We explain the importance of Overall Impact, what percentiles mean, and how to interpret summary statements.

Also included in this chapter is information on tracking your application and steps to take once you've received a response from NIH. You'll learn about just-in-time information and how to resubmit your application if it is not funded the first time around.

NIH REVIEW PROCESS: A BRIEF OVERVIEW

Once you have submitted your application to NIH, it goes through a few levels of review. First, the Center for Scientific Review performs a cursory assessment, checking for errors that automatically disqualify an application.

If there are no errors, the center sends your proposal to the group of reviewers known as the IRG. From there, your application goes to a study section (SRG).

The SRG is composed of roughly 20 scientists, mostly non-federal, who have expertise in relevant disciplines and current research areas. The scientific review officer (SRO), who is an NIH staff member, leads this group and appoints a few key reviewers to analyze your proposal in detail. The remaining members scan your application, reading only certain sections in depth.

The study section votes and scores your application on the five review criteria: Significance, Innovation, Approach, Investigator(s) and Environment. The group also evaluates your project's Overall Impact. The SRO compiles a summary statement that includes your application's scores as well as a more detailed critique.

After the SRG's assessment, your application goes to institute/center national advisory councils for review. Councils are composed of both scientists and lay members chosen for their expertise and activity relating to health and disease. Your application is only eligible for funding if both the study section and the institute/center advisory council recommend it.

NIH CHECKS YOUR APPLICATION

As soon as NIH receives your proposal, it goes to the Center for Scientific Review for a cursory review. The staff there makes sure it conforms with administrative and formatting requirements.

NIH calls this check a potential failure point because the agency may return your application without a peer review. This would happen if you:

- Didn't list other support
- Failed to include sufficient human or animal documentation, data, assurances, or other required documentation
- Omitted pre-approval documentation for submitting an application requesting \$500,000 or more in direct costs for any one year
- Left out pre-approval documentation for an investigator-initiated clinical trial
- Didn't show documentation of approval for using select agents
- Included a detailed budget when it should have been a modular one
- Improperly formatted your application (wrong font size and margins)
- Submitted the forms in the wrong way — for example, emailing them instead of submitting through grants.gov
- Didn't meet the requirements of a request for applications or institute-specific program announcement, if responding to one of the initiatives
- Contacted a reviewer
- Submitted your application late.

YOUR APPLICATION GETS AN NIH ID NUMBER

The Center for Scientific Review gives your application a unique identification number that looks like this: 1 R01 AI183723 02 A1 S1. Each part of the identifier provides a snippet of information about your application.

- The first number is the application type; for example, a new application is Type 1. This tells NIH whether your application is a new, renewal, noncompeting or other type of application.
- Next is the activity code, or the type of grant you've applied for; in your case, an R01 research grant.
- The next two-letter abbreviation is the institute code. For example, the National Institute of Allergies and Infectious Diseases code is AI.
- Next is the unique serial number Center for Scientific Review assigns.
- Then comes the suffix showing the support year for the grant.
- The final two are codes for a resubmission, supplement or fellowship institutional allowance.

In the eRA Commons, the website where you submit your application (<https://commons.era.nih.gov/commons/>), you'll see this NIH number. You'll also see the old grants.gov tracking number. But NIH staff will typically refer to your application using the NIH number.

YOUR APPLICATION IS ASSIGNED TO AN IRG, SRG AND INSTITUTE/CENTER

The Center for Scientific Review assigns your application to an IRG and then to a study section for the first round of peer review. It assigns institute/center advisory boards (sometimes more than one per application) for the next review level as well.

You can request review assignments in your assignment request form. But keep in mind the center is not required to honor your requests. It may make different assignments based on NIH referral guidelines and workload factors.

Within three weeks of your submission deadline, your assignment should appear in the eRA Commons. Here's how to access it:

Log in to the commons to check. If you don't see your assignments within three weeks, call the eRA Commons Help Desk at 1-866-504-9552.

At first, you might not see the expected study section. Instead, that field may show the umbrella organization, the IRG. This will be updated over the next few days, when your application is assigned to the SRG that will actually perform the initial peer review.

If the Center for Scientific Review gives you an assignment you're not happy with, you can request a change.

After the funding agency receives your application, it is assigned to a program division using internal referral guidelines. The program officer, grants management specialist and SRO fields will be blank initially in the eRA Commons.



REMEMBER:

You can request review assignments in your cover letter. But keep in mind the CSR is not required to honor your requests.

Call if You're Not Satisfied With an Assignment

Follow these steps if you are not happy with your study section or institute/center assignment:

- 1) Inform your SRO of the problem well before initial peer review begins. Speak up if a committee member has a conflict of interest or you feel the group doesn't have adequate expertise.
- 2) Check the Center for Scientific Review study section roster index to find an alternative.
- 3) Discuss the alternative you prefer with the chief of the IRG for your assigned study section. You can get his contact information from your SRO.
- 4) Fax a letter to the center at 301-480-1987 stating your reasons for requesting a change. Here is an example of an acceptable request and an unacceptable one:
 - a. Acceptable: "The focus of study section X seems to be more on the structural biology of molecules of immunologic importance. Since my application proposes to develop new antibodies for phase 1 human studies, the clinical perspective of reviewers on study section Y is critical to appreciate the approaches I have taken."
 - b. Not acceptable: "I don't want study section X due to lack of expertise Z."
- 5) If that does not resolve the problem, appeal to the Center for Scientific Review's director of receipt and referral by calling 301-435-0715.
- 6) Be sure to talk to your program officer about the situation.

Waiting for the next receipt date is often better than getting reviewed by the wrong study section. You also have grounds for an appeal if the group doesn't have the expertise required for an effective peer review and, as a result, the assessment turns out poorly.

SUBMITTING ADDITIONAL INFORMATION

You may add certain information to your submitted application, even though it's sitting in the eRA Commons database waiting for review. But there are restrictions on what you can add, guidelines on how to add it, and a deadline you should know.

NIH policy allows you to submit new material up to 30 calendar days *before* the peer review meeting. But only material that results from “unforeseen administrative issues” is acceptable. This includes:

- **Relocation information.** If you accept a job at a new institution or a new position with your current organization, you can write a letter notifying NIH of that.
- **Issues from natural disasters.** For example, notify NIH if flooding damages the lab where you plan to conduct your research.
- **Letters of support.** If you decide to change key personnel and add a collaborator, you may submit a letter of support from that person.
- **Biographical sketch changes.** If an investigator suddenly leaves or you hire new lab personnel, you can alter Biographical Sketches.
- **Articles.** If publications were in press when you turned in the application, but they've now been accepted, you want to let NIH know.
- **Budget revisions.** For example, say you require the same piece of equipment for overlapping grant proposals, and your other grant was funded. You can submit a budget revision removing that equipment from the proposal about to be reviewed.

The SRO will determine whether your information will be included with your application. Post-submission materials NIH will not accept include:

- Support letters that don't result from a key personnel change
- Updated Research Strategy or Specific Aims pages
- Late-breaking research findings.

These guidelines will apply to all unsolicited, investigator-initiated applications. There are exceptions, however, for certain Funding Opportunity Announcements, training grants and Requests for Applications.



TIP:

NIH policy allows you to submit new material up to 30 calendar days ***before*** the peer review meeting.

Follow These 5 Steps

There are essentially five steps to the post-submission process.

- 1) Contact your institution's Sponsored Programs Office or Sponsored Research Office.
- 2) Secure the NIH-required signature from the signing official at your institution. NIH won't accept materials that are sent without it.
- 3) Follow NIH guidelines for the pages you're submitting. For example, updates or changes to a Biographical Sketch or a budget will require a form page. If a form page is not needed, however, NIH guidelines indicate you must limit each letter or explanation to one page. Also remember to follow NIH policies regarding margins, paper size and font size.
- 4) Prepare a description of the material you're submitting. If you're sending data, as an exception to one of the grant mechanisms listed above, you should:
 - Design a concise table or graph to represent the data.
 - Succinctly describe the experiment's design, results and conclusions.
 - Indicate the significance to the proposal.
 - Note results that will add to the proposal's innovative nature.
 - Use a bullet-point format.
 - Include the grant number and title.
- 5) Send the post-submission material to the SRO. NIH prefers you send the information electronically as a PDF. You should include:
 - A note to the SRO with a brief description of your attachment
 - One or two sentences about why you are submitting it
 - The grant number and title
 - All post-submission materials in one email.

If the SRO accepts your material, it will be uploaded to eRA Commons. You'll be able to find it by checking the "Additions for Review" section of your application.

INITIAL PEER REVIEW

Direct from NIH:

Your application's most significant test is initial peer review. Your peers — successful scientists in your field and related ones — use the information in your application to assess the merit of the science you've proposed and your ability to get the work done. Peer review results in a numerical value indicating the reviewers' judgment of the likelihood that your project will have a powerful impact on its area of science. That number is the most important factor in determining your application's success.

How SRGs Operate

The SRG is made up of scientists who have expertise in relevant scientific disciplines and current research areas. Each study section is led by an SRO, who is a staff scientist with the NIH's Office of Extramural Research. The SRG also has a chair, who serves as moderator for discussing applications' scientific and technical merit and is a peer reviewer.

Study sections are typically composed of about 20 reviewers. It is their duty to:

- Declare conflicts of interest with specific applications following NIH guidance
- Receive access to the grant applications approximately six weeks prior to the peer review meeting
- Prepare a written critique (using review critique fillable templates) for each application assigned per the SRO, based on review criteria and judgment of merit
- Assign a numerical score to each review criterion
- Make recommendations concerning the scientific and technical merit of applications, in the form of final written comments and numerical scores
- Make recommendations concerning protections for human subjects; inclusion of women, minorities and children in clinical research; welfare of vertebrate animals; and other areas as applicable for the application
- Make recommendations concerning appropriateness of budget requests.

Federal officials who are not part of the review board are allowed to attend review meetings. But they must have advance approval from the responsible SRO. These individuals may provide programmatic or grants management input at the officer's discretion.

What SROs Do

Direct from NIH:

Your SRO does an initial check of your application to make sure the key parts are there. If you're responding to a request for applications, program staff will check to ensure it is responsive to the request for application.

Before sending your application to reviewers, SROs look at it more thoroughly to make sure it's complete, and they may contact you if anything is missing. If this happens, send in the information quickly so reviewers receive it well before the review.

The SRO ensures each application receives an objective and fair initial peer review, making certain all applicable laws, regulations and policies are followed. The officer performs the following tasks:

- 1) Analyzes application content and checks for completeness
- 2) Documents and manages conflicts of interest
- 3) Recruits qualified reviewers based on scientific and technical qualifications and other considerations, including:
 - a. Authority in scientific field
 - b. Dedication to high-quality, fair and objective reviews
 - c. Ability to work collegially in a group setting
 - d. Experience in research grant review
 - e. Balanced representation
- 4) Assigns applications to reviewers for critique preparation and designation of individual criterion scores
- 5) Attends and oversees administrative and regulatory aspects of peer review meetings
- 6) Prepares summary statements for all applications reviewed

The SRO selects at least three reviewers to examine each proposal and report on it to the rest of the study section. These individuals are highly influential in how the SRG grades each application. In fact, for your grant to score well, all three must become enthusiastic advocates of your proposal.

The assigned reviewers are typically those panel members who are most familiar with your area of research. If none of the members have the necessary expertise, the SRO will find at least one ad hoc reviewer with the appropriate credentials.

In most cases, the primary reviewer will be best acquainted with your work and will take the lead in presenting your application to the panel. The second reviewer will likely be nearly as familiar, having published in the same field or a related one.

These two reviewers will scrutinize all aspects of your research plan carefully, taking into account significance, feasibility and innovation, as well as your qualifications to perform the proposed work. With their expertise, they are positioned to decide whether your planned studies will significantly advance the field, rather than merely provide incremental progress on an already well-characterized system.

The third reviewer, who is often called the “discussant,” is usually different. He will probably not be an expert in your field but will have a general knowledge of it. For example, the discussant may have learned about your field by teaching certain aspects of it in a survey course. For this person, the crucial part of your proposal will often be the “Significance” section.

The discussant will look for details regarding specific ways your research, if successful, will affect fields other than your own. Consequently, the better you can establish that your findings will have important implications at large, the more likely this reviewer will appreciate your work’s significance and convey enthusiasm for your research to the study section.



REMEMBER:

The SRO selects at least three reviewers to examine each proposal and report on it to the rest of the study section.

BASIC LAYOUT OF INITIAL PEER REVIEW

The peer review process has four steps:

- 1) Applications are reviewed based on established criteria.
- 2) Assigned reviewers summarize their prepared critiques for the group.
- 3) The entire panel discusses the application.
- 4) Final scoring of Overall Impact/priority scores is conducted by private ballot.

After the SRO opens the meeting, the primary reviewer presents your application to the group. Those with conflicts of interest should have already left the room. The remaining individuals review applications in the order of their preliminary Overall Impact scores, which helps them calibrate final scores. This also helps reviewers gauge when it is appropriate to stop discussing applications, as they generally do not discuss about half of the applications.

At that point, the group decides if other applications merit discussion. They explore differences of opinion, interacting heavily during the discussion, which generally lasts 10 to 15 minutes. Other study section members ask the assigned reviewers questions and skim the application during the discussion.

Generally, once the group has found a fatal flaw everyone agrees to, they stop discussing the application. Examples of fatal flaws include not protecting the safety of lab workers or animals, proposing too much work for the award time, not recognizing a key paper in the field or including a factual inaccuracy.

Where possible, study sections evaluate applications from new and early-stage investigators before the more experienced researchers. That way, the SRGs review at least half of applications for new investigators, and NIH can meet its targets for funding them. Review materials are confidential, so reviewers are not allowed to divulge any information outside the meeting. At the end of the meeting, NIH staff collect and destroy all materials used in the review.

Most Reviewers Scan Each Application

Generally, only assigned reviewers will read your application before the review. Others mostly read just your Abstract, Significance and Specific Aims. SRGs receive dozens of applications for each meeting, totaling thousands of pages to read in a few weeks, and members have full-time jobs. They couldn't possibly read all applications in depth.

Keep in mind that all of the study section members will score your application, even though only a few will have read it in depth. That's why you write and organize your Specific Aims for both audiences. You must make a strong case for your research so the assigned reviewers can readily read, understand and explain your project to the group.

HOW REVIEWERS SCORE APPLICATIONS

Before the SRG meets to discuss the applications, each reviewer and discussant assigned to an application gives a separate score for the five criteria — Significance, Investigator(s), Innovation, Approach and Environment. In addition, they assign a preliminary Overall Impact score to an application. Applicants will receive a report or summary statement detailing the individual scores of the assigned reviewers and discussant(s), even if the full committee does not discuss the application.

Noncompetitive Applications Get a Streamlined Review

Direct from NIH:

NIH uses a process called “streamlining” so reviewers can focus on applications that have a chance of being funded. Review committees don’t review any application the group unanimously feels is roughly in the bottom half of applications being reviewed at the meeting. That percentage varies by grant type as well as by study section. Because no institute funds 50% of applications assigned to it, there’s no need to review the bottom half. Here is how streamlining works:

- One week before the study section meets, SROs ask members for a list of applications they feel should not be reviewed and prepare a combined list.
- If any reviewer disagrees with a call, the group will review that application.

Non-Numeric Scores

- 1) Not discussed (ND). Applications unanimously judged by the peer review committee to be less competitive are not discussed. These applications do not receive a numerical impact/priority score, but they do receive individual criterion scores. No set number of applications is discussed; in some meetings, the ND option may not be used.
- 2) Not recommended for further consideration (NRFC). A majority of reviewers must vote in favor of NRFC for an application to be designated as such. Members will vote for NRFC in the following scenarios:
 - a) The application lacks significant and substantial merit.
 - b) The project presents serious ethical problems regarding the protection of human subjects.

c) The research poses serious ethical problems in the use of vertebrate animals, biohazards and/or select agents.

NRFC-scored applications do not proceed to the second level of peer review (national advisory council/board) because they cannot be funded.

3) Other non-numeric scores

a) Deferred (usually due to lack of sufficient information, quorum or to allegations of research misconduct)

b) Abstention (used rarely)

c) Conflict (score put in by a reviewer who is in conflict with the application)

d) Not present

Competitive Applications: Five Criteria Determine the Score

The reviewers and discussant(s) assign scores for the five criteria related to your proposal's scientific and technical merit. The scores are based on the 1-to-9 scale. Your application does not necessarily need to be strong in all categories to be judged likely to have major scientific impact. For instance, a project that is not necessarily innovative may be essential to advance a particular scientific field. Now, let us examine the five individual score criteria used to evaluate your grant proposal.

Significance

For this criterion, reviewers determine if your proposed project addresses an important problem or a critical barrier to progress in your field. They also examine how scientific knowledge, technical capability and/or clinical practice will be improved if you achieve your project's aims. And they seek to understand how successfully completing the proposal's aims will change the concepts, methods, technologies, treatments, services or preventive interventions that drive the particular field.

Investigator(s)

This criterion represents the PI's qualifications. If it involves early-stage or new investigators, reviewers want to see experience and training. If the researchers are established, the SRG will look for an ongoing record of accomplishments that have advanced the fields involved. And if the proposal includes collaborative or multiple

PIs, investigators should have complementary and integrated expertise. They must also have a leadership approach, governance and organizational structure that is appropriate for the project.

Innovation

The study section wants to see that an application challenges and seeks to shift current research or clinical practice paradigms by using new interventions, instruments, theoretical concepts, approaches or methodologies. The SRG wants to ensure that these factors are new to one research field or new in a broad sense. And the reviewers look for refined, improved or new applications of interventions, instruments, theoretical concepts, approaches or methodologies.

Approach

Approach represents a proposal's overall strategy, methodology and analyses. Reviewers want to ensure these aspects are well-reasoned and appropriate for accomplishing your project's Specific Aims. Address any potential challenges, alternative strategies and benchmarks for success. If the project is in its early stages, the Approach should include a strategy to establish feasibility and manage any particularly risky aspects of the research. If the project involves clinical research, the Approach should delineate plans for protecting human subjects from research risks and plans to include minorities, members of both genders and children. It should also include any justifications of the proposed scientific goals and research strategy.

Environment

Reviewers want to ensure that PIs will have the resources — the institutional support, equipment and other physical assets — they need to successfully complete the proposed research. Additionally, the SRG wants to know if there are any unique features of the scientific environment, subject populations or collaborative arrangements that will benefit the project.

Role of the Review Criteria

Direct from NIH:

Peer reviewers don't score applications strictly by the review criteria; rather, the criteria are gauges for assessing merit and feasibility. Your assigned reviewers give your application a score for each criterion as well as the whole application; other reviewers score just the whole application. It's important to understand how review criteria relate to your score:

- Overall impact and merit. A final score reflects a judgment of the likelihood of a project to have a powerful impact on its area of science.
- Ideal application. To a large extent, reviewers judge your application based on their ideal outstanding application in your field of science. This is similar to a dog show, where dogs are judged for “best of breed” and different breeds do not compete with each other. So there is not a one-to-one relationship between how your application measures up to the review criteria and your score.
- Usage varies. Adherence to the criteria varies by committee.
- Weight varies. An application does not need to be strong in all review criteria to get a high Overall Impact score, though all criteria can affect your score. Two examples: Reviewers may assign an exceptional score to a proposal for important work that is not innovative but is essential to move a field forward. An application with high significance may receive an outstanding Overall Impact score even if reviewers are less enthusiastic about the other criteria.



REMEMBER:

The Overall Impact reflects the SRG's assessment of the likelihood that your project will exert a sustained, powerful influence on the research field(s) involved based upon the five review criteria.

Assigning an Overall Impact Score

The Overall Impact reflects the SRG's assessment of the likelihood that your project will exert a sustained, powerful influence on the research field(s) involved based on the five review criteria. The study section arrives at an Overall Impact score by following these steps.

- 1) Before the meeting, the assigned reviewers score each criterion and determine a preliminary Overall Impact score.
- 2) The discussion may prompt them to change their initial score.
- 3) The SRG votes. Assigned reviewers enter their official scores for each criterion and an Overall Impact score on the vote sheet. The other members can see these and give an Overall Impact score (and usually have an option of scoring each criterion).

Overall Impact Scores Range From 1 to 9

The SRG uses the preliminary score to determine which applications the group will discuss in full. Each member’s score reflects his evaluation of the Overall Impact the project likely will have on the research field(s) involved, rather than being a calculation of the reviewer’s scores for each criterion.

The scoring system uses a nine-point scale. The Overall Impact score for each discussed application is determined by calculating the mean score from all the eligible members’ impact/priority scores and multiplying the average by 10. The final Overall Impact score is reported in the summary statement.

Use the following table to understand Overall Impact scores:

Impact	Score	Descriptor	Additional Guidance on Strengths/Weaknesses
High	1	Exceptional	Exceptionally strong with essentially no weaknesses
	2	Outstanding	Extremely strong with negligible weaknesses
	3	Excellent	Very strong with only some minor weaknesses
Medium	4	Very good	Strong but with numerous minor weaknesses
	5	Good	Strong but with at least one moderate weakness
	6	Satisfactory	Some strengths but also some moderate weaknesses
Low	7	Fair	Some strengths but at least one major weakness
	8	Marginal	A few strengths and a few major weaknesses
	9	Poor	Very few strengths and numerous major weaknesses
Minor weakness — An easily addressable weakness that does not substantially lessen impact Moderate weakness — A weakness that lessens impact Major weakness — A weakness that severely limits impact			

Percentiling

Your Overall Impact score will be expressed on your summary statement in a percentile. This is the approximate percentage of applications that received better Overall Impact scores from the SRG during the past year. Keep in mind that only a portion of all applications receive percentiles because different NIH institute/centers assign them to different types of applications. And your summary statement will identify the base that NIH used to determine your percentile.

Direct from NIH:

For appropriate applications — certain activity codes or request for applications — scores will be percentiled to the appropriate base (e.g. study section base if the number of R01 applications > 25; CSR-all or IC-all base if <25). All percentiles are rounded to a whole number. Until a base has been established from three rounds of review, percentiles are based on less than three application rounds.

ADDITIONAL REVIEW CRITERIA

In addition to the five scored criteria and the Overall Impact, there are other aspects of your application reviewers consider. Depending on their applicability to the proposed research, the SRG will evaluate the following additional items while determining scientific and technical merit and the Overall Impact/priority score.

But the study section does not assign the following elements a separate score:

- **Protections for human subjects.** This is for research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46. Reviewers evaluate the justification for involving human subjects and the proposed protections from research risk according to the following five review criteria:
 - Risk to subjects
 - Adequacy of protection from risks
 - Potential benefits to the subjects and others
 - Importance of the knowledge to be gained
 - Data and safety monitoring for clinical trials.
- **Inclusion of women, minorities and children.** If your proposal involves clinical research, the committee will evaluate your application for inclusion of minorities and members of both genders, as well as whether it includes children as potential subjects. There is a federal law (Public Law 103-43) that requires women and minorities to be included in all NIH-supported clinical research projects involving human subjects unless a clear and compelling rationale establishes that inclusion is inappropriate. Similarly, NIH requires that children — defined as those younger than 18 years of age — be involved in all human subjects research supported by the agency unless there are scientific or ethical reasons for excluding them.
- **Vertebrate animals.** The review committee also evaluates your proposal for any involvement of live vertebrate animals according to the following five points:

- Proposed use of the animals and species, strains, age, sex and numbers to be used
- Justifications for the use of animals and for the appropriateness of the species and numbers proposed
- Adequacy of veterinary care
- Procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research, including the use of analgesics, anesthetic and tranquilizing drugs, and/or comfortable restraining devices
- Methods of euthanasia and reason for selection if not consistent with the American Veterinary Medical Association *Guidelines for Euthanasia*.
- Biohazards. Reviewers assess your application to determine if any materials or procedures proposed are potentially hazardous to research personnel and/or the environment and, if needed, determine whether adequate protection is proposed.
- Resubmission (A1). When reviewing a resubmission application, which was formerly known as an amended application, the review committee will examine the application as presented, taking into consideration the responses you made to comments from the previous scientific review group and changes made to the project.
- Renewal. When examining a renewal application, which was formerly called a competing continuation application, the reviewers will consider the progress you have made in the more recent funding period.
- Revision. For a revision application, which was once called a competing supplement application, the committee considers the appropriateness of the proposed expansion of the project's scope. If the revision relates to a specific line of investigation in the original application, the committee will consider whether your responses to comments from the previous SRG are adequate and whether any substantial changes are clearly evident.

There are also certain elements that, if applicable to your proposal, reviewers will consider, but again, they will not score them individually. These include:

- An application from a foreign organization. The SRG will assess whether the project will further research programs by using unusual talent, resources, populations, or environmental conditions that are either not readily available in the United States or augment existing U.S. resources. Reviewers generally do not comment on the foreign component of domestic applications as part of this consideration, but any remarks will appear with those about the application's Approach section.
- Select agents. The study section will assess the select agent(s) to be used in the proposed research; the registration status of all entities where select agent(s) will be used; the procedures for monitoring possession, use, and transfer of select agent(s); and plans for appropriate biosafety, biocontainment, and security of the select agent(s).
- Resource Sharing Plans. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that the results be made readily available for research purposes to qualified individuals within the scientific community. Reviewers will comment on whether the Resource Sharing Plans, which include experimental data, model organism, and genomic information, or the rationale for not sharing these types of resources, are reasonable.
- Authentication of Key Biological and/or Chemical Resources. Applicants should briefly describe the methods they plan to use to authenticate key resources based on their scientific experience and judgment, referencing relevant standards where applicable. Reviewers will comment on the plans for resource authentication in a manner consistent with the scientific goals of the research.
- Budget and period support. Reviewers will consider whether your budget and requested period of support are fully justified and reasonable in relation to your proposed research.

SUMMARY STATEMENTS

Once the study section has scored your application, the SRO prepares a summary statement. The document includes bulleted critiques from your assigned reviewers, a brief summary of the discussion, your Overall Impact score, your percentile, the SRG's recommended budget, human and animal subjects codes, and any administrative comments.

If your summary statement has an issue with human subjects, animals, or biohazards, NIH will assign it a code that prevents your application from receiving an award. The agency can't give you funding until you resolve the issue, so contact your program officer immediately.

Note that a summary statement is not an exhaustive critique. It is not a teaching tool containing every point reviewers found to be problematic in your application. But you can use it to revise a fixable application, if necessary.

Frequently Asked Questions About Summary Statements

Direct from NIH:

Q. How have summary statements changed?

A. The order of the review criteria has changed: Investigator(s) and Approach swapped positions; the new order (for research applications) is Significance, Investigator(s), Innovation, Approach and Environment. A table at the beginning of each critique summarizes the reviewer's scores for each criterion.

Q. How are the criterion scores displayed in the summary statement?

A. Criterion scores are added automatically by the Internet-Assisted Review (IAR) system as a table at the beginning of each reviewer's critique.

Q. What if the scores in the table do not agree with scores that may have been entered with the written critique?

A. The scores that IAR inserts in the table are accepted as final. Reviewers are instructed not to enter scores with their critiques and that errant scores in the critiques may be removed in finalizing the summary statement.

If You Have Additional Questions



STRATEGY:

If problems are fixable, start revising quickly. If your application misses the payline or is not discussed and its faults are fixable, start revising as soon as you can, because you may not have much time to revise after you get the summary statement.

You can contact the appropriate awarding component program official, whose name is in your summary statement, to ask any questions. The contact can:

- Discuss the review outcome of the application and give guidance
- Provide feedback and answers to any questions about the summary statement
- Explain the meaning of a numerical designation pertaining to human subjects or vertebrate animals in the summary statement
- Relay the funding status of an application

Direct from NIH:

Applicant investigators must not communicate directly with any review group member about an application either before or after the review. Failure to strictly observe this policy will create serious breaches of confidentiality and conflicts of interest in the peer review process. From the time of assignment to the time the review of your application is complete, applicant investigators must direct all questions to the SRO. This individual is in charge of the review group and is identified in the eRA Commons.

SECOND LEVEL OF REVIEW: INSTITUTE/CENTER ADVISORY COUNCIL OR BOARD

Once the SRG has weighed in on your application, the institute/center's advisory council or board performs a second review. The boards are made up of scientists from the extramural research community and public representatives who are approved by the U.S. Department of Health and Human Services. The President of the United States also appoints members for certain committees.

During this second review process, NIH staff examine applications, Overall Impact scores, percentile rankings and summary statements. They provide the advisory board/council with a grant-funding plan. The board considers the institute/center's goals before advising the director, and the director makes the final funding decision.

Applications that do not fall within the current payline but are aligned with NIH's priorities are placed on the "select pay" list. NIH staff create this list, prioritize it, and present it to the advisory board. If there is money left over at the end of the funding cycle, these selected applications will be funded in the order listed.

If your application receives an award, you will be working closely with the institute/center program officer on scientific and programmatic matters and a grants management officer regarding budgetary or administrative issues.



REMEMBER:

During the second review process, the advisory board/council considers the institute/center's goals before advising the director, who makes the final decision.

WHEN YOU CAN EXPECT TO HEAR BACK

Your scores will be available in the eRA Commons three business days after the review is complete. Your summary statement should appear there within three weeks, although it is usually available earlier for new investigators.

Tracking Your Application

Direct from NIH: https://grants.nih.gov/grants/tracking_application.htm

The eRA Commons provides a valuable resource for applicants and Principal Investigators to track an application throughout various phases of the grants process. Within the eRA Commons, the Status tab is where most of the tracking information is found. References to “Status” on this webpage are referring to the Status section of the eRA Commons.

- **Use eRA Commons to track status.** eRA Commons provides status of your grant application and allows you to review detailed information associated with your applications/grants.
 1. Login to eRA Commons with your Username and Password
 2. Click the Status tab on the blue navigation bar across the top of the screen
 3. Find the application/grant of interest
 4. Click on the Application ID. The Status screen contains the most current status and relevant documents for that application/grant.
- **Watch for email notifications.** Email notices are sent to notify the Principal Investigator and/or Signing Official to check the eRA Commons for a change in status.
- **Track throughout the grants process.** eRA Commons Status is updated throughout the NIH grants process.
 - **Tracking during “Planning, Writing, Submitting” phase.**
 - **Electronic submission.** Any errors or warnings identified during the electronic submission process are reflected in Status. Status also is used to access the final assembled application (called e-Application in the Other Relevant Documents section) that will be shared with reviewers.

- **Paper submission.** Applications must be submitted through the US Postal Service or another courier. Most couriers provide on-line tools to track packages.
 - NIH staff will manually enter data from your application into eRA Commons . Then eRA Commons can be used to electronically track your application through the rest of the grant process.
- **Tracking during “Receipt/Referral” phase.** NIH staff will assign your application to a review group and to one or more Institutes/ Centers (ICs) for funding consideration. The assignment and the contact information for the Scientific Review Administrator (SRA) will be reflected in Status.
- **Tracking during “Peer Review” phase.**
 - **Score and percentile.** Following the review group meeting, any available score and percentile information can be found in the Application Information section of the Status screen.
 - **Summary Statement.** Approximately 3 weeks after the review meeting a full Summary Statement is available in the Other Relevant Documents section.
- **Tracking during “Pre-award” and “Award” phase.**
 - **Just In Time (JIT)** (http://era.nih.gov/services_for_applicants/application_tracking_and_award/just_in_time.cfm). Some application information (Other Support, IRB and/or IACUC Approval dates, Human Subjects Education information) is requested just prior to a final award decision. If needed, NIH will send a request for this information. You may use the “JIT” link under Actions in Status list of applications/grants.
 - **Notice of Award (NoA)** (http://era.nih.gov/services_for_applicants/application_tracking_and_award/status.cfm). The NoA is the official grant award document notifying the grantee and others that an award has been made and stating the terms and conditions of the award. You will find a link to the NoA under the Other Relevant Documents section of the Status screen. NoAs can also be automatically e-mailed to the grantee organization. Organizational officials can maintain an NoA e-mail address in the eRA Commons Institutional Profile.

- **Tracking during “Post Award Management” phase.** Several post-award tasks can be managed through the eRA Commons .
- **Research Performance Progress Report (RPPR)** (<http://grants.nih.gov/grants/rppr/>). Progress reports are required annually to document grantee accomplishments and compliance with terms of award. They describe scientific progress, identify significant changes, report on personnel, and describe plans for the subsequent budget period or year. The RPPR is required for all awards issued under the Streamlined Non-competing Award Process (SNAP), and all F awards.
- **Closeout** (http://era.nih.gov/services_for_applicants/reports_and_closeout/grants_closeout.cfm). Electronically submit required Closeout documents including Final Status Report (FSR), Final Progress Report, and Final Invention Statement. At the appropriate time, a “Requires Closeout” link is available under Actions in your Status list of grants.
- **No-Cost Extension** (http://era.nih.gov/services_for_applicants/reports_and_closeout/no-cost_extension.cfm). You can extend the final budget period of the project one time for up to 12 months beyond the original expiration date on your NoA as long as no cost or scope change is involved. At the appropriate time, an “Extension” link is available under Actions in your Status list of grants. This may be completed electronically up to one day prior to the end of the project period.

Note: At this time written notifications of no-cost extensions are still accepted. However, such notifications must be received by the assigned NIH grants staff at least 10 days prior to the end of the project period.

Additional extension requests beyond this initial request require NIH prior approval and must be submitted in writing to the award’s assigned NIH grants staff.

Summary of Contacts:

eRA Helpdesk: Contact the eRA Helpdesk for issues related to the electronic grants process.

Prior to Review: Contact the Scientific Research Administrator referenced on your notification of assignment

Pre- and Post Award: For programmatic questions or concerns, contact your assigned Program Official. For administrative questions or concerns, contact your assigned Grants Management Officer. These assignments are found in Status.

JUST-IN-TIME INFORMATION

NIH may request just-in-time information if your application scored roughly within the top 20 percent. Although you may not get funded, you should prepare this information anyway. Ensure it is accurate and current.

Notify NIH of any substantive changes to previously submitted just-in-time information up to the time of an award, including changes in PI or key personnel status, as well as the use or approval of vertebrate animals or human subjects.

Other support information is always just-in-time. The funding agency also requests any of the following documentation relevant to your research that you did not include in your application:

- 1) Human subjects
 - a) Assurance number
 - b) Certification of institutional review board approval of research plan
 - c) Certification of human subjects education
- 2) Animals
 - a) Animal welfare assurance number
 - b) Certification of institutional animal care and use committee approval
- 3) Human embryonic stem cells (hESCs)
 - a) Identify the hESC line from the NIH Human Embryonic Stem Cell Registry

Other Support Submission

As a just-in-time filing, you'll need to send a list of other financial support — existing funding you have and any you may gain from the current application. If you have no other source of aid, your funding agency will need a letter from your institution's business office stating that fact.

Have any support information ready well before the award is made. It should show the following:

- No other organization is supporting the research you outlined in your plan: scientific overlap.
- Your time is not committed more than 100 percent: commitment overlap.
- You have not requested funding for items paid for by another source: budgetary overlap.

End-of-Year Warning

Funding agencies may skip over your application if it comes up for funding at the very end of the fiscal year and your just-in-time submission is not ready.

Your institution's business office should submit other support and human subjects training information within two weeks of receiving a just-in-time notice. You don't need to sign this information because you have a signature assurance on file with your institution. Because institutional review board and institutional animal care and use committee certifications may take more than two weeks, your business official may submit these approvals at the earliest date possible.

Whether you send the certifications with your application or as a just-in-time filing, they should be sent together. NIH prefers that your institution submit the documentation through the just-in-time feature of the eRA Commons in PDF format.

RESUBMISSION (A1)

Nearly every PI who submits a proposal to the NIH is denied the first time out. In fact, the estimated first-time rejection rate is 75 percent or more. Fortunately, NIH allows resubmissions for R01 proposals, and an estimated 35 percent of resubmitted applications get funded. The trick is knowing how to revise your application in a way that improves your funding chances.

Direct from NIH: <https://grants.nih.gov/grants/policy/amendedapps.htm>

A resubmission is an unfunded application that has been modified following initial review and resubmitted for consideration.

- You may resubmit after a new, renewal, or revision application, as specified by the funding opportunity announcement.
- We allow only one resubmission for each new, unfunded application.
- You may submit an unfunded new application as new again, without a resubmission.
- Before a resubmission application can be submitted, the PD/PI must have received the summary statement from the previous review.
- You must resubmit within 37 months of the application it follows. Thereafter, the application must be submitted as a new application.
- After an unsuccessful resubmission, you may submit the idea as a new application.
- A resubmission has a suffix in its application identification number, e.g., A1. (Resubmissions were previously called “amended” applications, hence “A1”.)
- **The NIH will not accept duplicate or highly overlapping applications under review at the same time, except in certain limited circumstances.**

Application Requirements for Resubmission Applications

- You may need to make significant changes to the resubmission, compared to the new application that it follows.
- You must include an introduction for all resubmission that:
 - summarizes substantial additions, deletions, and changes to the application
 - responds to the issues and criticism raised in the summary statement
 - is one page or less in length, unless specified otherwise in the FOA or is specified differently on our table of page limits. (http://grants.nih.gov/grants/forms_page_limits.htm)
- You may choose to submit an introduction for individual components of a multiproject application; it is not required at the component level.
- A resubmission of a revision uses the same one page for all introductory information.
- Career development and fellowship applicants must arrange for resubmission of the three reference letters required for those programs.

Policy Details

Reminders Related to the NIH/AHRQ Policy for Application Submission:

NOT-OD-15-059 (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-059.html>)

Clarifications to the NIH and AHRQ Policy for Application Submission: NOT-OD-14-082 (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-082.html>)

Overlapping applications: NOT-OD-09-100 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-100.html>)

Overlap with another application pending appeal of initial peer review: NOT-OD-11-101 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html>)

Time limit of 37 months for resubmissions: NOT-OD-12-128 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-128.html>)

History of NIH's policy on resubmissions: <https://grants.nih.gov/grants/history-of-resub-applications.htm>

Recent Policy Change

In April 2014, a significant change occurred within the NIH's resubmission policy. In the previous policy if a resubmission was unfunded the application had to be substantially different in both content and scope in order to be eligible for submission as a new application. The current policy allows for ideas that were unsuccessfully submitted as a resubmission to be presented in a new grant application without having to substantially redesign the content and scope of the project. This policy change from the requirement that previously reviewed applications be substantially redesigned in order to be accepted as a new application is in response to researcher's concerns that changing the scope to be accepted as new resulted in many meritorious research ideas being deemed ineligible for resubmission. It was argued that this previous policy was especially hard on new investigators, since finding new research directions can be quite difficult during this phase of their career. Likewise, established investigators expressed concern about the need to redirect the research focus of productive labs in order to submit future NIH applications.



REMEMBER:

Not counting the introduction, a revised proposal must keep to the same page limits as other proposals.

Is Resubmitting Worthwhile?

Before you begin revising your application, ask yourself if resubmitting is worth it. Will you be rewriting more than half of the proposal? If so, creating a new one might be a better use of your time.

Have you pursued the research and continued to gather results, or did you move on to something else? Revising and resubmitting takes time and commitment, so the research should be meaningful to you. You may want to start over with a different project, a different institute or program, and/or a new deadline.

Identify the Reasons for Rejection

If you decide to revise and resubmit your proposal, your first step is to identify the reason(s) for rejection. Carefully analyze the peer reviewers' summary statements. Read them more than once so you can identify your application's specific weaknesses and strengths. Look for critiques mentioned multiple times.

You will likely see a pattern of issues you need to address in your resubmission.

In a case study of 605 rejected NIH proposals, researchers found three areas that attributed to rejection the most:

- 1. Approach: 73 percent**
- 2. Problem: 58 percent**
- 3. Investigator: 55 percent**

Other reasons included institutional setting, unrealistic budget requests, inadequate personnel, lack of PI time, unconvincing project and sloppy presentation.

Respond to Reviewers' Comments

You have no control over issues with your institution, and you can't bend administrative, regulatory or agency guidelines. But you can respond to reviewers' comments about your approach, problem, experience, budget requests, personnel, overall project and presentation.

Outline the changes made to the resubmission application in the Introduction attachment. The NIH removed the requirement to identify 'substantial scientific changes' within the text of a resubmission application. Include a summary of substantial additions, deletions, and changes to the application as well as a response to the weaknesses provided in your Summary Statement.

Tips for Resubmitting

Get second opinions. Once you receive your reviews, you should seek out colleagues for their feedback on the reviews. They can be particularly helpful in advising on resubmission and ways to resolve problems identified in the comments. The most important second opinion you get may be from your program officer; they will better be able to tell you if you have an innovative idea worth pursuing in a resubmission.

Provide sufficient evidence to justify your project. Include specific background data. Highlight compelling new data you gathered while waiting for the initial response, and cite newly published research papers. Ensure your outcomes/objectives are measurable, obtainable and specific. Be sure to connect your research to its impact on the field and create a clear budget narrative.

Your Personnel Statement. With some imagination and creativity, there are ways you can use this statement to increase your chances of successfully being awarded funds. Make sure to describe your experience related to the subject matter being proposed in the application. In so doing, you must strike a balance between describing accomplishments and appearing boastful.

Focus on your writing. Create a strong introduction that keeps reviewers engaged and sets your proposal's tone. Be sure to label the progression of ideas, and keep your narrative concise by writing in short sentences and paragraphs.

Familiarize yourself with review process changes. Take note of new requirements like page limit reductions, and adhere to them.



REMEMBER:

It is important to read the initial RFA or program announcement you applied under carefully to see if there are any special rules regarding A1 resubmissions.



TIP:

The revised proposal requires a one page introduction that explains how the investigator has revised the grant.

CONCLUSION

This final chapter describes the review process, from receipt of your application by the NIH to ‘just in time’ procedures in the event that an award may be made to you. The information that you can expect to receive, as well as the timing of when to anticipate this information becoming available, is also described. The NIH realizes that you spend a lot of time getting to this point and they strive to keep you up-to-date with your application’s progress. Remember that the majority of applications received by the NIH are not awarded. So, if your application is not funded the first time around, shake off the initial disappointment, heed the reviewer comments, and submit again. ■

Appendix A: R01 Checklist

PREPARATION

- Your research idea matches NIH's stated goals
- Your research idea matches the goals of one of NIH's Institutes, Centers or Offices
- Your institution qualifies for NIH support
- The R01 is the right grant mechanism for your proposal
- Generate a focused, testable hypothesis
- Write a provisional title
- Choose the date to submit your application
- Create a writing schedule

PROJECT SUMMARY/ABSTRACT AND PROJECT NARRATIVE

- Review individual ICO requirements and include the required information
- Use proper formatting
- Stay within length requirements
- Include the following in your Project Summary:
 - Brief background of the project
 - Specific aims, objectives or hypotheses
 - Proposal's significance and relevance to public health
 - Project's unique features and innovation
 - Methodology
 - Expected results
 - How results will affect other research areas
- Use storytelling tactics to engage reviewers
- Examine samples from winning grants

BIOGRAPHICAL SKETCH

- Use the NIH form
- Determine Senior/Key Personnel
- Use Personal Statement to briefly describe why your experience and qualifications make you particularly well suited for your role
- In Positions and Honors, list your previous positions in chronological order, concluding with your present one.
- Try to list no more than 15 peer-reviewed publications or manuscripts.
- For Research Support, list both selected ongoing and completed research projects, beginning with the most relevant to the current proposal.
- If you're an early-stage investigator, stress your independence from others at your institution.
- Write a desired draft of a letter of support for the person to review and sign, but do not make all of your supporting letters look the same.

ENVIRONMENT

- Explain what facilities you will use.
- Detail how the scientific environment in which you perform your research will contribute to your success.
- For early-stage investigators, outline the following:
 - Institutional investment in your success
 - Collegial support
 - Logistical support
- If multiple sites are involved, describe the resources available at each site.
- List your available equipment
- If applicable, generate your Data-Sharing Plan, Sharing Model Organisms Plan and/or Genome-Wide Association Studies Plan.

RESEARCH PLAN

- Keep Specific Aims to one page.
- Follow individual NIH ICOs' instructions for crafting your Specific Aims.
- Make sure your Specific Aims are not sequential. If they are, show that you are prepared for unexpected results.
- Break your Specific Aims down into three sections: rationale, experimental approach, and outcomes and alternatives.
- In the Significance section of the Research Strategy, include the following:
 - Importance of the problem or critical barrier to progress in the field your project addresses.
 - How your proposal will improve scientific knowledge, technical capability and/or clinical practice.
 - How your project will change concepts, methods, technologies, treatments, services or preventive interventions.
- For the Innovation section, explain the following:
 - How your proposal challenges and seeks to alter current research and clinical practice standards.
 - New theoretical concepts approaches or methodologies; instrumentation or interventions you plan to develop or use; and how these are better than existing ones.
 - Refinements, improvements or new applications or theoretical concepts, approaches or methodologies, instrumentation or interventions.
- In the Approach, include the following:
 - Overall strategy, methodology and analyses you plan to use to accomplish your Specific Aims.
 - A statement of how you will enhance the reproducibility of your research findings through increased scientific rigor and transparency.
 - Potential challenges, alternative strategies and benchmarks for success.
 - For early-stage projects, any strategies to establish feasibility and how to change any high-risk aspects.
 - Any hazardous procedures, situations or materials and precautions you will use to address them.

- Provide preliminary data to support your proposal.
- Include a simple impact statement to each of the core criteria sections.
- Complete the Inclusion Enrollment Report.
- Cite your Bibliography and references.

SPECIAL CONSIDERATIONS

- Prepare your Protection of Human Subjects document and use subheads to delineate the four sections.
- Provide a justification if you plan to exclude women, minorities and/or children.
- Include your Data Safety Monitoring Plan.
- Provide the Inclusion Enrollment Report.
- Address the five points of the live vertebrate animal test subjects section.
- For Select Agents, complete the three points for each research site where the agents will be used.

BUDGET

- Ask only for enough money to do the work you propose, but do not “low ball” with an unrealistic budget.
- Review the cap for your grant mechanism.
- Choose your budget type: modular or detailed.
- If you’re using a modular budget, generate the needed justifications:
 - Personnel
 - Consortium
 - Additional
- For a detailed budget, complete the 11 separate sections on the application.

REVIEW YOUR PROPOSAL FOR CONTENT

- Your Project Summary/Abstract should describe all major aspects of your project.
- Ensure your budget accurately reflects the resources you need and expenses you will incur.
- Make certain your Research Strategy addresses Significance, Innovation and Approach.

ASSESS WRITING QUALITY

- Have colleagues review your proposal for clarity.
- Perform your own proofread, looking for misspellings, grammatical errors, etc.
- If necessary, hire a professional editor.

INCLUDE ALL NECESSARY COMPONENTS

- SF424 (R&R) (Cover component)
- Research & Related Project/Performance Site Locations
- Research & Related Other Project Information
- Research & Related Senior/Key Person
- PHS398 Cover Page Supplement
- PHS398 Research Plan
- PHS398 Vertebrate Animals Cover Page Supplement (New)
- PHS398 Checklist
- PHS398 Modular Budget or Research & Related Budget, as appropriate
- PHS398 Cover Letter File (optional)
- Research & Related Subaward Budget Attachment(s) Form (optional)
- Attach appendix materials as PDFs (no more than 10).

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About the Consulting Editor — Dorothy E. Lewis, PhD

Dr. Lewis has had continuous NIH funding since 1985, experiencing both times of multiple grants and reduced funding. She is a member of the AIDS Immunology and Pathogenesis study section (2007-2011) and became chair in 2009. She is thus very familiar with the new NIH application system and new methods of review, which focus greatly on impact. She has more than 140 publications, a few book chapters and reviews. And she has mentored many graduate students, fellows and other faculty members in grant writing, both in a formal course on the subject in the 90s, and then as the chair of the mentoring committee for the Center for AIDS (BCM/UTHEALTH), which was recently renewed in its fourth cycle.

Currently, Dr. Lewis is supported by NIH via an R37 that examines T cell dysfunction in HIV patients, the abovementioned CFAR as the Immunology core director, and a grant that examines how HIV might affect fat differentiation with a colleague at BCM. She is also supported by Novartis to develop a method to enrich fetal DNA from the maternal circulation for the purpose on noninvasive genetic diagnosis. She teaches medical students and graduate students at UTHEALTH and mentors various predoctoral and postdoctoral candidates, including in fellowship and grant writing.

Dr. Lewis received her PhD in Microbiology in 1978 from the University of Arizona in Tucson. She then did an NIH-supported postdoctoral fellowship at the University of New Mexico School of Medicine in Albuquerque under the mentorship of Dr. Noel Warner. She worked on an autoimmune model in mice trying to determine which immunologic abnormalities were genetically associated.

She became acquainted with flow cytometry during her fellowship and used instruments in Los Alamos to characterize murine T and B cells.

She was on a chartered study section from 1992-1996 and then participated in multiple review panels related to HIV or flow cytometry in the 1990s. She served on the NIAID council from 2002-2006 on the DAIDS subcommittee, which exposed her to policy matters and how topics are chosen by program.