NIH Short Form: Answers to 16 Frequently Asked Questions

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When NIH instituted the new short form grant application in January 2010, the agency provided little guidance regarding how to tackle the various sections of this instrument. Nonetheless, Principal Investigators have to use the form to obtain funding from the agency.

Listed below are 16 frequently asked questions directly from PIs just like you. And the answers have been provided by grant-winning experts with advice they have gleaned from years in the award-seeking trenches and serving as NIH reviewers.

Reader Question #1

What if Specific Aims 2 and 3 are dependent upon Specific Aim 1?

EXPERT COMMENTS

Then you must have an alternative strategy that offers another way to solve Specific Aim 1. For example, Specific Aim 1 involves a discovery phase use of mass spectrometry to identify the differentially expressed proteins in the blood of people with colon cancer. Because that's a discover-based Aim, it's going to succeed.

But let's say there's doubt that the mass spectrometry platform will have a sensitivity to get below an anagram per mil. Then you can have additional strategy, which could be an affinity reagent based for getting the sensitivity base below one anagram per mil.

As long as you have an alternative approach for the first Specific Aim — and it's a convincing alternative approach — then you can deal with the limitations of the alternative approaches in Aim 2. And the reviewers will understand your methods.

Reader Question #2

With the new short form application, NIH seems to be looking for more innovative rather than incremental research. But the truly innovative science doesn't get funded, or it seems to run into more obstacles. What is the real NIH stand here?

EXPERT COMMENTS

In many instances, the study sections set the tone for suggesting truly innovative proposals for funding, and some even establish special emphasis panels that call for innovation. That being said, you still have to convince reviewers that you can do what you say you are going to do. And that's easier if your approach is incremental over
work that has already been done.

One option is to have one innovative Specific Aim and one or two solid incremental aims that the reviewers know for sure will work and hope that you are playing both sides of the aisle. Potentially, you then get credit for thinking innovatively, but you have the reviewers’ confidence that they’ll get something for their money because you include two incremental Specific Aims.

The whole point of enhancing peer review, according to NIH, is to shake things up so that there is increased funding of innovative and decreased funding of incremental. That was explicitly stated policy behind the change to the new short form in 2010. Whether it will succeed is unclear at this time.

**Reader Question #3**

For early career investigators, the issue is, of course, independence from your former mentor. But demonstrating your independence if you have collaborators at other institutions can be problematic because you’re not in the same building, and there might not be much interaction. How should you effectively choose senior scientists as collaborators or mentors on a first time R01, and what are the different factors that go into that— independence versus having them available?

**EXPERT COMMENTS**

This has always been a thorny issue. NIH tells reviewers that they should not make snide comments about independents and to assume that if you applied as a principal investigator, then you are independent. They can question your qualifications to do the work, and demonstrated project management experience is a qualification that they’re allowed to evaluate.

As for picking collaborators, the issue — even for senior investigators — is that peer reviewers want to see that there’s a real collaboration and that it’s not in name only. The best way to demonstrate an ongoing collaborative interaction is to have published with the person that you’re naming as a collaborator. If you have, then there’s no question that the collaborative relationship has worked successfully. When you point to that joint publication, you demonstrate that despite geographical differences, you have worked together well in the past.

If you’re trying to start on your own and you’re in the same institution as your old mentor, you’re looking for collaborators to show that you’re independent. You have not yet published together, so what you need is a strong letter from the collaborator about his commitment to working with you and use your personal statement section, to outline a plan for promoting interaction between you and the collaborator, even though your distant. For example, you explain that you’re going to have weekly phone calls and that you’re specifically going to get together at a scientific meeting. You explicitly state your plan for frequent communication with your collaborator, and the collaborator notes this in their supporting letter. And that demonstrates that you’ve got a plan for making the collaboration work.
Reader Question #4

To get another set of eyes to review your proposal, how can you make sure that person is familiar with the new guidelines?

EXPERT COMMENTS

What’s most important about having someone review your proposal is finding holes in your logic, examining language to determine what’s confusing, or detecting flaws in your experimental design. Practicing scientists who have been trained and passed their thesis dissertation should be able to do this, regardless of whether they’re following the old or new guidelines.

They are looking for the logic. If you have a colleague who is a current peer reviewer using the new guidelines, he would be a great person to ask for help if he has time to read your proposal. The most important thing to uncover with an outside review is to check your writing’s clarity and the logical flow, and if you’ve made assumptions in your head that you did not put down on paper.

This reviewer could be somebody from an unrelated field. Remember that for some grant proposals, the third or fourth NIH reviewer might not be a person who’s working specifically in your field, but they may study in a similar area.

Just remember that some of the people reading your proposal may be outside your field, and your proposal must be clear enough that someone outside your field can follow it.

Reader Question #5

What grant application sections should new investigators pay particular attention to?

EXPERT COMMENTS

The new investigator should take advantage of the personal statement section because this is where you get to say, “This is what my training has been all about.” Use it to highlight what you learned in each of your post-docs and in your thesis project and how you’re going to apply them to your independent research career. You can outline your overall professional goals and clearly indicate that you have a scientific plan for yourself regarding problems you want to solve in the next five years. That will really give the reviewers confidence in your independence and in your professional motivation for what you do.

Then when you write the environment section, try to include details about your institution’s commitment. For example, your department chair offers to read your grant proposals and act as a grantsmanship mentor, or you’ve
gotten substantial release time from teaching so you can write your proposal. Your institution is using departmental funds to send you to a workshop or symposium to further your development. This shows that your institution is investing in you.

**Reader Question #6**

What is the best strategy for getting applications to the right study section?

**EXPERT COMMENTS**

The quick answer is to do your homework. Go to the Center for Scientific Review (CSR) Web site, and look at the mission statements for each of the initial review groups. Find the mission statement that best fits what you want to do and then do the following:

- Go to the roster
- Look at the investigators
- See what they’ve published
- See if they really can understand the type of research that you want to do
- Write a cover letter that indicates your grant proposal addresses a specific problem of interest to the study section.

The cover letter could go on to say that your proposal could best be reviewed by a specific institute or a study section. And you can provide as much detail as you need to get your proposal in the right hands.

But then you also should be careful regarding how you write your abstract. When your grant goes to CSR, they read your abstract and the cover letter and assign it to a study section. If you specifically ask for one or two study sections, your application will almost certainly go there. You should ask for two because if one study section is overloaded with too many applications, then at least you have a chance to get your second choice.

If you don’t write a cover letter, then CSR will assign your application based on the abstract. They will look for key words. If it says “cancer,” it’s going to go to the National Cancer Institute (NCI). If it says “biomarker,” it might go to “cancer biomarkers.” But if you really want to do a mechanistic study and you think your mechanistic study could implicate your protein as a biomarker you may find yourself in a biomarker section that might not like your mechanistic study.

The solution is to do your homework, write your cover letter and be extremely careful when you write your abstract or project summary that you have the right key words to direct your application to the study section you want.
Reader Question #7

If your institution does not have a track record in your research area, how should you bolster the environment sections?

EXPERT COMMENTS

Choosing collaborators who are strong in their fields is the best way to break into a new field that you or your institution hasn’t been in before. In the best case scenario, your institution offers a unique setting that you’re collaborator doesn’t have, but she wants access to because she can see its value.

The national lab system does this successfully because it’s good at developing instruments. But the U.S. Department of Energy (DOE), for example, does not fund biomedical research directly, and some of the national labs are in the middle of the desert and don’t have access to medical schools. The successful national labs have been able to get NIH-funded research by collaborating with a medical school or a major academic research center and bringing in that fundamental expertise and pairing it with the instrument development or the team science systems biology approach that national labs are known for.

Reader Question #8

Can one project receive support from multiple grants? If yes, how?

EXPERT COMMENTS

If you receive multiple grants, you will have to list your other support and possible areas of overlap, and the NIH accounting office will make sure that you don’t get paid twice for doing the same thing. But the projects may have varying scopes and how you define the project will depend upon the scope.

For example, your project is to develop a new therapy for a particular type of cancer. A part of that project involves structure-based drug design, and that could have a grant proposal that goes to chemists, biologists and computational people to actually design small-structural inhibitors based on structural biology. You also have a cell biology signal transduction group to determine the actual effect mechanism of a small-molecule inhibitor and the best target for small-molecule inhibitors within that signal transduction pathway. That would be a third grant proposal. Then you have to test it in a model, so you have to have a xenograph model, and that is a third part of the larger project with a third type of funding.

If you’re writing three different grants, you have to indicate how each part of that project is distinct and stands
apart from the others. This is like setting up a bookkeeping system to keep track of a pot of money that will support this activity, a second pot to support this other activity and a third to support a third activity. At the end, you must take the information from all three projects, and it achieves the overall goal of developing a new cancer therapy.

If you are an established investigator with the lab and you’ve been working on this research area for the past 20 years, you must use the support section to clarify the distinctions in the Specific Aims for specific projects.

**Reader Question #9**

For new investigators, what is an appropriate amount I should request? Will NIH consider hiring a post-doc appropriate?

**EXPERT COMMENTS**

To begin, each funding mechanism has a cap. A young investigator will almost never get permission to exceed the cap. For the small grants, the cap is $75,000 or $50,000 a year.

For an R01, the cap is $250,000 a year, so you should ask for what’s appropriate to your project. If you request $175,000 or $200,000 instead of $250,000, you show that you’re easing into the field and that could be a good thing. But if you’re doing human subject studies or animal studies, you may need the full amount because animals are expensive. So, explain in your budget request that animals are expensive, but that’s what you need to do the research.

As far as hiring a post-doc, NIH expects this for new investigators as well as for senior investigators. Ideally, reviewers like to see stability — an available technician shows that stability — and inexpensive bright young people are going to bring new ideas to the project. So a typical R01 does well with a post-doc and a part-time technician and 25 percent of the PI.

If your research involves soft money and you need to bring in 50 percent of your salary, then either a technician or a post-doc can make the difference. Either is acceptable, but strategically, you might consider using a part-time technician.
Reader Question #10

Innovation used to be an option. Is it still an option or is it a required section?

EXPERT COMMENTS

Innovation is no longer an option, but a required application section. In fact, it’s a criteria reviewers use to score your proposal. Even if it’s in a field where there has been little innovation recently, talk about why it was innovative five years ago to be able to develop this project, talk about the innovative approaches you’re going to use to demonstrate lack of toxicity, clinical ethic, etc. You have an unusually well-balanced team, and that's innovative. Or you’re going to use a new set of statistical tools to evaluate the outcome of your data.

But it is a required section. And “innovative” doesn’t necessarily mean new. It can mean what’s unique about your approach, and what sets you apart from everyone else. That goes in the innovation section.

Reader Question #11

Is there any advantage to being a brand new company rather than an established company?

EXPERT COMMENTS

Having a track record is always good, whether you’re an individual investigator, an academic institution or a biotech company. But a track record doesn’t always need to be associated with the company. It could be associated with the project’s PI who’s now formed his third biotech company in 10 years, and his prior two biotech companies are highly successful. That's a track record.
Reader Question #12

How should I approach the space constraints and preliminary data? Is it best to have everything published?

EXPERT COMMENTS

Always. You can’t include manuscripts on your application that were submitted. They have to have been accepted.

If you can reference a published article, then you don’t need to put the figure in preliminary data. If it hasn’t been published and hasn’t been accepted for publication, then you have to include it as preliminary data, and you have those tight page limits.

So, you now have to determine the most important piece of preliminary data needed to establish feasibility and the keystone piece of preliminary data that answers the largest number of questions. You may have had an experimental line of investigation where you had experiment A, then B, then C and then D. You had to solve technical problems in A to get B to work, and in B to get C to work, and in C to get D to work. So if you include Figure D and it was successful, and you point out that Figure D resulted from solving the problems A, B and C, you don’t have to include the actual data from A, B and C. If you have D, it proves you’ve done A, B and C. You have to take a good hard look at the preliminary data and prioritize.

Reader Question #13

If Specific Aims are dependent upon each other, where should I describe the alternatives?

EXPERT COMMENTS

In the Action Plan. The first page should show the logical flow between the Specific Aims. And if they are contingent upon each other, the flow between them will be on that first page.

If there’s a way to show an alternative in one sentence on the first page, yes, put it on the first page. But developing the clear either/or strategy and what the consequences of failure of the first steps would be for success of the Second Aim, should come in the Approach section of the Action Plan.
Reader Question #14

We have heard that NIH does not fund science that it considers “fishing expeditions.” How do you describe your project for hundreds of biomarkers for a specific disease like colon cancer so that it seems more focused on specific scientific leads instead of screening for elusive fish?

EXPERT COMMENTS

In the cancer biomarkers study section, the agency has established a special group to recognize that finding biomarkers requires gathering data before you can form a hypothesis. It’s a hypothesis-generating exercise opposed to a hypothesis-testing exercise.

If you’re going into a more normal study section and you feel that you need to generate data to generate an hypothesis, this is a fishing expedition. The problem is that people write proposals with a fishing expedition in them because they have a tool, such as a gene expression array, and they haven’t really thought about what they’re going to do with it.

So you should show that you have an overall strategic plan for solving a problem and that gathering this data is key to solving your problem. Then you have to have a data analysis approach that is targeted, focused and not just statistical. For example, you’re doing a systems biology approach, and you’re looking for protein/protein interaction. You hypothesize that protein/protein interactions will identify novel signal transduction paths. Now you’ve gone from conducting a fishing expedition to a hypothesis-generating expedition.

Keep in mind, however, that a great deal relies on what you’re going to do with the data once you have it and whether the problem you’re trying to solve really needs that kind of approach. For example, that type of work frequently gets questioned because people say, “I have this one protein, and I think it’s important in one carcinogenesis, so I’m going to study it. And, by the way, I’m also going to do a gene expression array.” In response, reviewers say, “Why do the gene expression array if you’ve already got a good target?” If you haven’t clearly indicated this in the application, the reviewer will not understand it?

The key to writing a Specific Aim that will allow you to generate large data sets is to make the scientific objective and focused analytical strategy for getting mechanistic information out of a large data set extremely clear and focused.
Reader Question #15

If there are project changes post-award, is there any mechanism to request supplements?

EXPERT COMMENTS

Yes. You should talk to your program manager. You will submit annual noncompetitive renewal applications or progress reports where you will inform the program manager what worked, what didn’t and what new opportunities are out there.

When you submit your annual noncompetitive renewal, your data is so exciting that it opens up a brand new area that you would like to explore, but you would like another $50,000 for making transgenic mice, for example. You could put that potential opportunity into your non-competitive renewal progress report and then call up your program manager. Your program manager will give you excellent advice as to whether you could try for a grant supplement or if you should simply put in a new R01. The program manager should help you find the right study section for that UR01.

Reader Question #16

How can I make a clinical proposal more attractive to a study section that primarily deals or is accustomed to basic science proposals?

EXPERT COMMENTS

Underscore the basic science knowledge that will command the clinical trial and frankly discuss the challenges of using human beings as animal subjects. There’s a basic science component to your clinical problem. Identify it. Acknowledge all the great basic science that went into your clinical hypothesis that you’re going to test and clearly state any limitations of doing experimentations with humans.

Have alternative strategies. Maybe you have to have access to 1,000 subjects to be able to identify 10 in category A and 10 in category B that you could’ve done if you used mice.
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