Executive Report

National Institute of Health Short Form Application

Easy-to-read how-to manual tailored to help you improve your grant success.

by

Karin Rodland, Ph.D.

&

Principal Investigators Association

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A Note from the Editor

Dear Professional:

Thank you for ordering NIH Short Form Application Executive Report from the Principal Investigators Association Library. This resource is designed to help you better understand – and make the most of – changes to the National Institutes of Health’s (NIH) grant application form.

Karin D. Rodland, PhD, served as co-author for this executive report, and we gratefully acknowledge her input. Dr. Rodland’s research is focused on mechanisms of signal transduction in normal cells and how those mechanisms are altered in cancer cells. Dr. Rodland has competed successfully for NIH grants for over 25 years and has been an NIH reviewer since 1998. Dr. Rodland’s professional experience includes over ten years as a chief scientist for biomedical research at a non-profit research institute and 17 years as a faculty member at Oregon Health Sciences University. She has been a member of the Oregon Cancer Institute and a collaborating scientist at the Oregon Regional Primate Research Center. You can contact Dr. Rodland at krodland@verizon.net.

In addition to the special reports that make up the library, Principal Investigators Association offers a weekly e-Alert, Principal Investigator Advisor monthly newsletter, and a year-long series of audio conferences – all devoted to helping you improve performance and spend more time doing what you love: the research. Our goal as an association is to be the world’s leading source of real-world, results-oriented information for our members in all fields of science. Our unique approach — delivering targeted guidance, case studies, success strategies, and best practices — has earned us a reputation for depth, usefulness, and high-value information as well as a loyal group of members who rely on that information to help them with their administrative and funding duties. We’re glad you’ve joined them, and invite you to review all of our products and services at www.principalinvestigators.org.
We are always on the lookout for interesting topics, researcher needs, and ways we can be of service to you. If you have a success story you’d like to share with your colleagues, please do not hesitate to contact me. I’d be thrilled to hear from you, and I look forward to serving you and your organization with the best advice and information available in the months and years to come.

Best Regards,

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Executive Summary

Changes to the main NIH grant application that have been in effect since January 25, 2010 — shortening the form considerably and changing somewhat its emphasis — have now undergone a full cycle of submissions by principal investigators and reviews by government reviewers.

Karin D. Rodland, PhD, member of the Oregon Cancer Institute and a collaborating scientist at the Oregon Regional Primate Research Center, says she hasn’t seen any problems at the review level. She emphasizes that “current NIH policy for review of the short forms, at least during this transitional period, is that submitters should not be penalized at the score level for failure to comply with the new requirements for the Biosketch and Resource pages.” However, “non-compliance should be noted in the Other Comments section of the review.”

Rodland reports that the NIH “wants to know if applicants are using sections outside the page limits — e.g., Human Subjects, Vertebrate Animals, Data & Resource Sharing — to circumvent the page limits by moving experimental details to those sections.” It’s always best, she says, to use the form in the way it was designed: as a shorter, more streamlined application process that’s focused on two key issues:

1. Will the research you’re proposing result in a clinically relevant product or a game-changing shift in your area of research?

2. Are you the best researcher to make that happen?

A good way to test whether your application answers those questions adequately, Rodland says, is to use the “elevator speech” as a template for the all-important first page of the new form, where you detail your specific aims.

Imagine you’re in an elevator with Bill Gates, and he has a billion dollars he wants to invest in research. Even if you’re going from the penthouse to the parking garage, you have about three minutes to convince him that what you want to do needs to be done — and that you can do it. That’s because most reviewers essentially make up their minds about the fundability of your proposal as they read the first page. Then they read the rest of the application looking for support for that original impression.
Use storytelling tactics to engage reviewers

Write your proposal as if you’re telling a story. You’re trying to get the reviewer emotionally involved to the point the he or she wants to see your project funded. All good stories have a resolution. Yours is how the field will be changed as a result of your research and how future research will be enabled by it. That’s the impact part. All grant proposals should end with a short paragraph that goes over the impact:

“At the end of the day, when this research is done, my field of research will be changed because we will know [fill in the blank] and we will then be able to go on and do [fill in the blank].”

It’s where you tell reviewers what happens next.

Those are the key points principal investigators should be aware of regarding the shortened grant application forms. Throughout the document, themes have evolved and specific points have changed.

The Introduction section, for example, was three pages and is now just one. That’s where you address prior reviewer comments if you’re resubmitting. Keep in mind that, now, you get only one chance to resubmit. So the introduction should be a big picture of what the major concerns of the original reviewers were and how you’ve addressed them — then you should refer the new set of reviewers to your revised document. It’s also where experienced researchers from the private sector can explain how their experience — likely not as familiar to reviewers as academic experience — translates to the NIH model.

Another change is in the section for your biographical outline. The NIH now requires that you add a personal statement detailing why your experience and qualifications make you well-suited for the project. It shouldn’t sound like boasting. Stick to relevant criteria, such as past presentations, grants, and publications. If you’re an experienced researcher but have never had an NIH grant, the Biosketch section is your opportunity to make it clear that you’re “new” — but not an early-stage investigator.
Show recent accomplishments on pubs list

Show clearly your independence from other researchers at your institution. Ideally, get a letter of support from your department head stating the institution’s commitment to your success. It's now suggested — but not required — that you limit your publications list to a total of 15. A good rule of thumb is to provide the five most recent, the five most important to your general field of study, and the five most relevant to the proposed research. How do you choose? Reviewers are always going to be most interested in what you’ve done lately. If those publications are directly related to the topic of the proposal, then all three categories are covered with your 15 most recent publications. But if they don’t demonstrate your strength as an investigator, go back to older publication and pull out five or six that do.

The Research Strategy section has been restructured

The old categories of Background and Preliminary Studies are gone, replaced by Significance, Innovation, and Approach.

Innovation can be an innovative idea, because you’re changing the paradigm, or it can be new instruments, methodologies, or interventions. While you need to give reviewers some context, focus mostly on what the challenges are and on what’s innovative about your approach.

You will continue to spend most of your time on Approach in the shortened form. You need to discuss specific problems, alternative strategies, and benchmarks for success. What reviewers are really interested in is your thought process. How likely is it your plan will work? And you have to tell them what you’ll do if you get an unexpected result in your first aim. Convince them there is still a future to your proposal.

Reliability matters because it addresses feasibility. NIH reviewers recommend discussing reliability and standard operating procedures in the Approach section — and in the Environment section if yours has a history of good lab practices or good manufacturing practices. Be extra careful about that if you’re applying for a competitive renewal and you’ve changed your specific aims. You have to tell the NIH why.
Research environment

There’s a lot more focus on environment in the new form. The new moniker is Scientific Environment and Probability of Success, and it’s now part of the Facilities and Other Resources section. With the new form, the NIH requires you to address how the scientific environment at your institution will contribute to your success. Highlight the features of your institution that make it a good place to do the research. Does it have a unique set of technical capabilities? Access to a specific patient population? A particular scientific emphasis?

In the Specific Aims section, make the logical flow of your proposal clear. The impact paragraph at the end of that page is a good place to point out whether your work can be used for other purposes.

Don’t try to cram in more information than a 12-page application can comfortably hold. You may be tempted to use densely written text — small fonts and small margins. Doing so will likely turn the reviewer off. There’s a difference, in reviewers’ minds, between “goals, objectives and aims” — even though all three terms are used in the Specific Aims section.

Goals are high-level: “Our goal is to understand signal transduction in breast cancer.” Objectives go down a level to something more specific. They are, in a sense, a restatement of your hypothesis. Aims are outlines of your tactics — the specific steps you’ll take.

It’s important to note that changes to the grant application are designed more for reviewers than for you. And reviewers are much more limited in how they can instruct you on improving future proposals. In fact, they’re specifically instructed not to. Rather, there’s now a special box at end of the review template labeled Other Instructions to the Applicant, which is where the reviewer can provide mentoring comments — like, “This would be better if you had a clinical collaborator.”

Overall, reviewers will respond best to a narrative. Bullet points and charts and graphs offer an excellent framework for an application, but they shouldn’t underpin it. Tell a story. And make it clear you’ve thought about the significance of what you’re doing.
User’s Guide to the New NIH Short Form Grant Application

Chapter I

The focus is now on the impact of your work; changes to the application emphasize offering a concise narrative of what you plan to discover and how it will affect your area of research.

According to reviewers, the National Institutes of Health (NIH) peer-review process had serious problems: Too many proposals were requiring a third submission before funding. So the NIH instituted a three-year review of the peer-review process. Much of the resulting changes to its grant application form attempt to capture what actually happens in review sessions, convey that information to you as an applicant, and make sure that your research proposal actually addresses the points that the reviewers care about.

Much of the information you’re now asked to provide was already there under the old forms; you just weren’t aware of where the reviewers were going to look for it. This document will explore the major areas of the short form that have changed from the longer version, how those areas have changed, and how you should change your application in response.

Potential ‘Impact’ of your work guides reviewers

Perhaps the biggest change from the old application to the new is the new form’s focus on Impact. A common question from applicants is, “What is ‘impact’ and how can I get some?”

Addressing the issue of Significance vs. Impact, the NIH instructed reviewers to evaluate significance by assuming that all of your experiments will work: “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, is supposed to include the likelihood that the experiments actually will succeed: “If they don’t work, there won’t be any impact, even if there is high significance.” (For much more information on the critical new element of impact in the short form, see Appendices A & C.) Reviewers have been instructed to weigh all of the individual core criteria on your application and come up with an overall impact score.

• Is your work innovative, or is it more of the same?
• Is it just incremental?
• Are you well-trained and well-equipped to do the project?
• Will your research environment actually support doing the project and getting the work done?
• Is your actual experimental design feasible, logical, and well thought through?
• Are problems addressed?
• Does the reviewer have confidence that that you’ll be able to do publishable work with the money that the government gives you and, at the end of the day, that your published work will be read and will make a difference in your field?

Reviewers use no magic formula in going from your individual criteria scores to your overall impact score. Each reviewer likely will rate those criteria differently. Some will base your Impact score almost entirely on your experimental approach, just as they always have. Others will be much more concerned with Innovation and Significance. It also will depend on the specific grant you’re seeking. The Impact score on an R21, for example, generally should be more about Innovation and significance. For an R01, on the other hand, that score ought to be based more on Environment and Approach.

Impact varies from grant to grant — SBIR review differs from R01

Weighing SBIRs (Small Business Innovative Research) and R01s, reviewers are looking for pretty much the same thing. The difference is the impact for an SBIR should be commercial; that is, you should detail a path toward a commercial application that is relevant to human health. In an R01, though, impact is further upstream and can be much more basic science-oriented. It doesn’t need to have a commercial application, but it may have one further down the line.

SBIR grants are funded from separate set-aside funds, so they don’t really compete with R01s and other kinds of grants. Because they’re different financial animals, grant applicants often have questions about the processes involved:

• Is there a special review mechanism for an SBIR grant?
• Do SBIR grant proposals get reviewed by the same study sections that look at grants from academic institutions?

• How are SBIR proposals viewed by reviewers in general?

There are a few standing study sections in the technology area that review SBIRs. In general, SBIRs are in response to program announcements and have special review panels convened particularly for those announcements and their objectives. The review panels will have a mix of academic reviewers and biotech industry research reviewers because the funding agency tries to have a breadth of perspectives, including a commercial one.

The review is much the same as an R01 gets, with the added criterion that a commercial path forward has to be obvious. Reviewers generally triage proposals, and the bottom half generally are not discussed. However, in some SBIR panels, reviewers will discuss applications all the way down to the bottom of the list because there are fewer of them.

You’ll get an overall impact score, which is a score of 6 or 7, instead of a score of 3 or 4. That’s one of the big differences in review. Applicants should note that SBIR reviewers say they often see a lot of naivete on basic-science issues on the part of very small companies submitting SBIRs, noting that, because those firms often are trying to accomplish a great deal of research, often with as few as three or four people, collaborations are important in their SBIR proposals.

‘Reliability,’ other uses of data can raise Impact score

Can something as basic as the reliability of your experiments impact their Impact? Yes, according to NIH reviewers. Reliability should be very clear in your Approach section because it addresses feasibility; indeed, some reviewers feel “reliability” is underappreciated. In the biomarkers area of research, for example, some scientists are coming to appreciate how important reliability and standard operating procedures are and that part of one’s proposal does get weighted more heavily. You might also discuss reliability in your Environment section, particularly if you’ve got a history of good laboratory practices or good manufacturing practices or your lab is CLIA (Clinical Laboratory Improvement Amendments)-certified.

Assume you’re proposing a clinical trial involving the pregnancy condition pre-eclampsia as one end point. The data you generate also could be used to study, say, miscarriage and pre-
term deliveries. If you want to play up some of the other uses of the data set, you should, in the Impact statement, mention that the effort going into establishing your patient set has relevance beyond the pre-eclampsia study and, once the metadata have been gathered, other studies — either subsequent studies that you do or that collaborators will do at their institutions — will make use of the resource to address other scientific questions. That's clearly related to Impact and so-called “bang for the buck.” Clinical trials are expensive. If you can use your data to do more than one study, you are much more likely to get your work funded.

**Biosketch now includes Personal Statement**

Another key change in the application is in the biographical sketch: The NIH now requires that you add a Personal Statement detailing why your experience and qualifications make you well-suited for a role in the project. NIH reviewers also suggest, but do not require, that you limit your publications to a total of 15. You still have a four-page limit to the entire biographical-sketch section.

One grantsmanship issue many applicants face is what to do with the new Personal Statement requirement. Reviewers will now consider that and use the information when they fill in the box on the investigator’s qualifications.

That’s why you need to give the reviewer specific information about your background — whether it’s your pedigree, your research experience, or your track record of being able to solve problems in new areas. You need to point out specifically why you think you are the most qualified person to lead the project you’re proposing. Avoid sounding as if you’re boasting, though. Rather, reference specific objectives and criteria in your background, grants you have already been awarded, and publications that came out of those grants.

Presentations you’ve given or were asked to give can be referenced as well. You can address the issue of changing fields of study and, if you are a new investigator but not an early-stage one, your experience working in a national laboratory. If you’ve been out there for years but never had an NIH grant, the Personal Statement is where you make it clear that, while you are new, you are not an early-stage investigator. It’s an important distinction reviewers need to know.

Reviewers are instructed now to be less stringent about preliminary data if you’re an early-stage investigator because you haven’t had the resources for three to five years to do
preliminary research. Keep in mind that reviewers would rather judge you on your track record as a post-doc than as a graduate student. Be sure to bring your track record forward in your personal statement.

‘Experience’ need not be solely in academic research

Here’s a case-study example: A principal investigator returns to academia from a successful career in, say, the biotech and pharmaceutical industries at the executive level, having managed budgets up to $100 million a year. Prior to that, the PI was, say, in the NIH Intramural Program for 10 or more years and was awarded tenure at the NIH decades ago. The PI in this example is also a member of the Institute of Medicine. However, the PI has never received an NIH grant because funding always came from other sources. In that sense, the PI is a new investigator. What’s the best way to leverage your background in obtaining funds if your situation matches elements of that example?

Know that experience counts a lot — and that you need to make yours explicitly clear. The Personal Statement is the place to do so and, by referencing things in it like your membership in the Institute of Medicine, your having achieved tenure in a very competitive environment, and your having been given responsibility over projects that merit $100 million in funding, you can demonstrate your competence and experience and track record in a way that’s relevant to NIH reviewers predominantly from academia.

You would qualify for the new-investigator category under this scenario. But, with your experience, you won’t receive many breaks. Still, you may be given some leeway in terms of presentation because reviewers will recognize that you’re not used to following the NIH format. You’ll be judged like the senior investigator you really are.

If you’re an actual early-stage investigator, it’s important to address your independence from others at your institution if you’re staying there for the work you want the government to fund. So, in your Personal Statement, you should put something like, “Although I did my post-doctoral training here, I have moved on to independent status with my own lab space. I’ve been the intellectual force behind the project for the last year. I wrote the grant proposals. My former mentor is going in a different direction.” Having a letter from your former mentor would be very helpful, reinforcing the fact that you are independent, delineating the differences between what you’re doing now and what your mentor is continuing to do.
Use Personal Statement ‘creatively’

The new Personal Statement section offers applicants the opportunity to clarify who does what — and who pays for what — in a series of experiments involving multiple personnel and funding sources. Here’s a for-instance: Say a renewal R01, where part of the K01 of a junior investigator — on which the PI of the R01 is the sole mentor — has overlapping aims, and the K01 mainly supports salary and not all the support infrastructure. The R01 will have many more aims, although some will overlap. Should the K01 recipient be listed as a Significant Co-investigator or Other Significant Contributor if no salary is requested?

Because the K01 is a training or transition grant, you’d simply need to explain the relationship between the K01 and the parent R01 in the Personal Statement — and possibly in the Environment statement, because, the K01 recipient is a positive feature of the environment. The K01 PI should be an investigator/key contributor in such a scenario and should explain the relationship in his or her Personal Statement. You should explain the salary support issue in the Budget Justification section.

Another example: Assume you have a K award and will very soon be submitting an R01 application that builds on the data you’ve collected as part of it — a small RCT (randomized controlled trial) on a treatment you developed, for example. Should you emphasize your status as an early-career and new investigator? Should you also emphasize how the pilot data were collected as part of the K award? And, specifically, where in the application should you discuss that — and how much space should you dedicate to it, given the new format and space limitations?

The official directions for the new Personal Statement indicate that it should reflect why you’re uniquely qualified to do the proposed work. Thus it’s an appropriate forum for discussing your background, which should clearly reflect your status as both an early-stage and a new investigator — one who has 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 make it clear how your prior work is directly related to, and clearly supports, the work you propose in the R01. Highlight your ability to think strategically: What is the next question? What is the next proposal?
As for the space allotted, you have four pages and approximately 15 publications to list, so there should be ample room. A template provided by the NIH devoted about two-thirds of a page to the Personal Statement, but the range is probably a half-page to a full page. In addition, experimental results from a K award that contributed directly to the hypotheses of the R01 application or that demonstrate the feasibility of what you propose also should be highlighted in the Research Strategy section. It is permissible, and probably advisable, to have a specific Preliminary Studies section within the Research Strategy section. For a 12-page proposal, that section should be about three pages. Don’t be afraid to use the phrase “Work completed under the K award demonstrated that …” or “Based on work funded by the K award, we hypothesize that …”

New guidelines limit number of publications to list

NIH reviewers encourage you to limit your publications to 15 — and they suggest you include your five most recent, five most important to your field, and the five most relevant to your proposed research. One of the issues many applicants face is how to pick the top 15. Many have 50 or 100 or more published papers. First, reviewers always will be interested in what you’ve done lately, so they’re going to want to see what you’ve done over the last five years, whether that means five papers or 10. If what you’ve done most recently is directly related to the topic of your proposal, all three categories are covered with your 15 most recent publications. But if you think your 15 most recent don’t really demonstrate your strength as an investigator — say you had a bad year, changed institutions, or had a personal setback — you should go back into your older publications and pull out five or six that demonstrate:

- that you’ve worked in the field before;
- that you’ve had a track record of being successful in several different fields; and
- that you’ve been able to make an impact in your field.

The new publication limitation guidelines have sparked many questions from applicants, such as whether adding additional publications will upset reviewers and whether applicants should go to the trouble of including all the PubMed Central identification (PMCID) information for each publication. Many of your colleagues also want to know whether an appendix should include only publications that are “in press” or whether already-published papers should be
included so they’re readily available to the reviewers. The answers to those questions:

- Few applicants have limited their publication list to 15, and reviewers haven’t, apparently, been too irritated by it. But reviewers stress that you should identify those publications you think are most relevant to the current proposal, even if you go beyond 15. Reviewers do get “irritated,” according to one, when they have to scan through a list of 56 pubs to find the three that actually relate to the topic at hand.

- As for adding the PMCID code: It’s the law. The NIH could “withdraw you administratively,” in government funding agency parlance, if you don’t.

- There’s also a regulation about papers in the appendix. You are to include only papers that are not publicly accessible on the Internet, so, clearly, that limits you to “in press” manuscripts not yet published online.

Another way to approach the publication limit is the scenario where more than 15 publications are listed without bumping the Biosketch page total to more than four. What would R01 reviewers think? Would their response change if you, the principal investigator, or your co-investigator/key personnel, had extensive research experience, a strong history of federal grant awards, and a long list of related publications?

If you have a strong track record and history of funding and publication, it is particularly important to set aside the 15 most relevant, impactful, and recent articles, to spare the reviewer the necessity of wading through a very long list. In such cases, you can afford to leave the rest of your references out, simply stating, “15 most relevant of 225 published over the last 20 years” — or words to that effect. If you think you have 20 or 30 references highly relevant to the proposal, then certainly include them — but be selective.

The publications list also is a chance for you to demonstrate that you have a track record. R21 and R03 grant proposals are limited to six pages, and R01s and similar types of proposals are limited to 12. Obviously, with fewer pages, you don’t have as much space to go into detail on the background of your field, experimental detail, or to go into 35 figures of preliminary data. The push now, under the shortened application form, is to be able to reference your published papers that demonstrate feasibility and your track record and to reproduce only those figures that have not been published and that demonstrate key points — either the key scientific points
that establish the validity of your hypothesis or the key technical points that demonstrate the feasibility of your approach.

The publication list is an ideal place to show previous collaboration with the co-investigator you’ll be working with under the grant. NIH reviewers characterize as “very important” showing that you have a track record of working with the collaborators you bring together, and they note that the publication list is “one of the cheapest places to demonstrate that.”

You’re better off sacrificing some of your more impactful publications to include a few that show that you’ve worked with those collaborators. You can add a sentence that says, “This team includes collaborators who have worked together in the past and published X number of papers, as demonstrated below.” Reviewers have seen many collaborative proposals shot down because they feel there’s insufficient evidence that the researchers have worked together. What if one of you is in Philadelphia, and one’s in Washington? Reviewers want to know you’ve already found ways to bridge the geographical divide.

**Significance, Innovation now part of Research Strategy**

The research-plan section of the grant application has been restructured considerably. The old categories of Background and Significance, Preliminary Studies, Progress Reports, and Research Design and Methods all have been lumped together in a section called Research Strategy, with Significance separated out as a separate section. Innovation has been added as a specific section.

Note that you can be “innovative” because your idea is innovative, because you’re changing the paradigm and the way you look at a problem, or because you’ve got new instruments or methodologies or techniques for your invention. Innovation can come from the idea, it can come from the preliminary data, or it can come from the tools that you’re going to apply to the problem. But you must make that point to reviewers.

Under Research Strategy, you should call out a specific subheading for Significance and one for Innovation — and you likely will want to have a subheading for Preliminary Studies as well. The NIH leaves it up to you whether to submit it aim-by-aim or in a section by itself, but your reviewers will be most comfortable seeing it in a section by itself because that’s the way they’re used to seeing it. So that tends to be the more effective approach.
However, as you’re writing your proposal, it will become obvious to you if you’re describing an aim and you need to show a particular piece of preliminary data to establish that the aim is feasible. The data discussion could go within the discussion of that aim or it could go within a big section on Preliminary Data, referencing back to it in a specific aim: “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,” for example. It’s up to you.

There are no required page limits for the subsections under research strategies, but the NIH does suggest 10% to 15% for Significance, 15% to 20% for Innovation and Impact, 25% for Preliminary Data/progress report, and 33% to 50% for Approach.

**Reviewers focusing more on where you work**

Environment has been added to Facilities and Other Resources. 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 reviewer characterizes it, “the only place that a reviewer could find information about the environment was the list of centrifuges and computers, which is really not very helpful.” Now, under the new application form, the NIH requires you to address exactly how the scientific environment at your organization will contribute to your probability of success.

List the unique features of that environment that make your lab the best place to do the research you propose. Features may include a unique set of technical capabilities, access to a special patient population, the collaborative nature of interactions between you and your colleagues. Or a particular emphasis on, say, neurobiology.

You also have to tell reviewers specifically why you’re the most qualified person to do the project. For early-stage investigators, reviewers look for evidence of institutional support, some measure of how valued your research is by your institution, and its level of commitment to helping you succeed.

It’s often difficult for a principal investigator to succeed on a first proposal. You often need assistance, whether in the form of start-up funds, access to graduate students, or departmental support for training, travel, or a career-enrichment program. Whatever it is, reviewers want to know that your institution has made an investment in you.
Here’s an insider tip: Reviewers may be skeptical of your application in you’re an early-stage investigator working at the same institution as your post-doc — and nearly in the same area — when your post-doc mentor still has active grants. A reviewer may wonder if the funds might find their way indirectly to the mentor instead of funding a young investigator. You need to demonstrate that you are independent and that the research you propose is your project.

Reviewers also may be skeptical of a situation where you’re a long-term post-doc and your institution offers to make you a research assistant professor — if you get a grant. They want to see that your institution has already made you a research assistant professor, not that it’s making its commitment to you contingent upon your getting the grant. Be sure to address your independence in the Environment section if you’re an early-stage investigator.

**Innovation takes on new importance**

The NIH wants you to show how what you’re doing is innovative. Provide the context of what is already known about an area, and what the challenges are. You can accomplish that with a brief, concise background section. Then make it very clear what’s new and innovative and groundbreaking about your approach.

You’ll see there are multiple bullet points under the Significance and Innovation headings. You do not need to make each a header and address each in your proposal. Of course, some reviewers are quite meticulous about reading all of your materials and matching point-to-point. But those reviewers often have been reviewing for a few years and they expect to see what they’ve seen before.

The bullet points are good guidelines for you to respond to. If you have covered all of them, you can be confident that you have covered a thorough Significance section or a thorough Innovation section. But don’t organize your information by bullets or by subheads. Rather, provide a narrative, demonstrating that you’ve thought about the significance of what you’re doing, that you’ve thought about how your approach is different from others.

Be aware that some reviewers will focus their Innovation attention on the techniques you use, to the virtual exclusion of other innovative consideration. There is still a way to emphasize the innovative components of your application if your work is based on applying established techniques in an innovative way to solve an important problem.
The best approach in that situation is to 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 the day. If you have been truly innovative in applying established techniques, you will have a unique set of data that addresses a previously unanswered question — and therein lies your innovation.

**New Approach section minimizes reviewer commentary**

Approach is addressed in the new Research Strategy section as part of an effort to make reviewers be less wordy, to prevent them from restating your specific aims and going on about the technical approach you’ll use — because you already know that, and if a reviewer writes that in your review, he or she isn’t helping you change your application. Rather, reviewers are instructed to talk about how they’ve evaluated your likelihood of success and how they’ve given you useful feedback.

Reviewers are directed not to give you instructions on how to change your application — certainly not in the five core review criteria that contribute to the overall impact score. There’s now a special box at the end of the review template that says, Other Instructions to the Applicant. That’s where a reviewer might give you some mentoring comments — such as, “This proposal would really do better if you had a clinical collaborator.”

But that’s not supposed to contribute to the overall score because the next reviewer who gets your amended application may not see the problem in the same way. Some applicants try to change their proposals in response to reviewers’ directions only to find that the next set of reviewers doesn’t like the changes — they liked your original proposal more. With the new forms, the NIH is trying to stop that vicious cycle.

Approach is what you’ll spend most of your time on and what reviewers will spend most of their time evaluating. They’ll look especially carefully at potential problems, alternative strategies, and benchmarks for success. If your project is in the early stages, you should describe your strategy to establish feasibility and address the management of high-risk aspects of the proposed work. That’s a very important aspect of Approach.

Reviewers don’t want to see details of which restriction enzymes you’re going to use and which buffer goes with what restriction enzyme or the brand of mass spectrometry you’re
going to use. What they’re really interested in, especially with the fewer pages, is your thought process:

- Have you thought carefully about the problem you’re trying to solve?
- What is your initial plan of attack?
- How likely is that plan of attack to work?
- What are the possible things that could go wrong?
- What aspects of feasibility have you not yet demonstrated?
- And what’s your plan for dealing with those problems if the experiments don’t work out?

Note that, if you’re demonstrating the feasibility of recruitment of a target sample size in a psychosocial treatment outcome study, you’ll want to discuss your ability to recruit X number of participants in both the Environment/Resources section and in the Approach section. The ability to recruit adequate numbers of patients is that crucial to clinical studies. Use one sentence in the Approach section to document annual patient accruals and/or past successes in recruiting patients, then go into slightly more detail in the Environment section about why your institution is such a good place to do clinical studies.

Also, for studies with non-standard, non-trivial “data analysis” needs, be sure to describe those needs in sufficient detail in the Approach section to inspire reviewer confidence. With a 12-page limit, use about a half page for that — or up to one page if the data analysis is really complex and integral to your success. If your project is a biomarker study or clinical trial, know as well that the NIH will assign statisticians to your proposal specifically to evaluate the statistical design and power issues, which must be discussed in the Approach section.

Those issues are also a key component of the Vertebrate Animals section, because you must justify the number of animals you will use. Using too few to get a statistically valid result is considered to be bad form, as is using too many. Protection of human subjects, on the other hand, is its very own section outside the page limits. Be sure to address that seriously, as your proposal will automatically hit the “Not Discussed” bin if reviewers feel your discussion of human subjects issues is inadequate.

The Approach section also can house details on novel aspects of your work. Example: You
want to use a better, more innovative, method of calculating sample size that reviewers are unlikely to be know. Are you better off sticking to more conventional sample-size calculations? Or should you put the more sophisticated method in an appendix? Neither, actually. Instead, reference a publication that explains the new method for calculating sample size, and stick to a brief description of its advantages in your Approach section. If there really needs to be a large chunk of explicative text, try getting the Scientific Review Officer’s permission to submit it as supplemental material, once you have your study section assignment.

**Many reviewers will base funding on Specific Aims**

The Specific Aims section now stands alone. It is the most important one page in your entire document. Many reviewers will read it and make up their minds immediately whether your work is worth funding. Then they will read the rest of the proposal looking for specifics to reinforce their initial opinions. If they initially decide that they like your proposal, they’re likely to look for supportive points they can put in their review. If they immediately decide they don’t like it, they might begin to search for faults.

If a reviewer reads the first page, finds it interesting but remains unconvinced, he or she likely will read the rest for the feasibility issue. Therefore be sure to end that first page with a short paragraph that states the impact of your work — how your field of research will be changed if your project succeeds.

A comment reviewers often make is, “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 reviewer what you intend to do if you get an unexpected result with Aim 1. You have to convince the reviewers that there is a future to your proposal nonetheless.

If you are doing a competitive renewal and changed the thrust of your research from the original proposal five years earlier, tell reviewers why you changed the specific aims, and detail your new directions. That’s because the reviewer will see the summary statement from the initial award and know what the specific aims were originally. Some reviewers are very
particular about that. “Did the PI succeed in the first five years?” If not, some reviewers will opt not to fund you for a second chance. If you changed direction because something came up that was more interesting to pursue, or a new technology became available, you need to inform the reviewers as to why you changed directions.

Reviewers Differentiate among Aims, Goals, and Objectives

Note that the terms Aims, Goals, and Objectives are used in the application, often seemingly as synonyms. But they have separate meanings. Goals are strategic and high-level: “Our goal is to understand signal transduction in breast cancer.” Objectives go down one more level: “The objective of this proposal is to understand the role of the EGF receptor axis in the proliferative response of breast cells to … whatever.” The objectives in a sense are a re-statement of your hypothesis, in a way that can be falsifiable. Your hypothesis might be that the EGF receptor axis is key in mediating steroidal effects on proliferation. Your objective, then, is to determine the mechanism by which that occurs.

The aims are the outline of your tactics. “Aim 1 is to establish a culture system of primary breast epithelial cells,” perhaps. Aims could also be tasks. They’re something that you can point to at the end of the year and say, “I have accomplished this aim.” In other words, goals are the 30,000-foot view, objectives are the 10,000-foot view, and specific aims are the 1,000-foot view. Whether each aim has its own hypothesis in addition to an overall hypothesis is a matter of individual style. What is important is to make sure that the logical flow is clear.

This is also important: Never force a hypothesis on experiments that are not truly hypothesis-driven. A statement like “We hypothesize that a comprehensive analysis of plasma proteins 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 a statement like, “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.” It’s a critical difference.

Also, unless your project is “discovery research,” it is very important to have a specific, falsifiable hypothesis, and to state it explicitly. Whether you have a general, overarching
hypothesis that covers the entire proposal or a specific one for each aim is a question of personal style and of what best fits the science you are proposing. But there should be a hypothesis somewhere in your application. Again, though, don’t force a hypothesis. Vague statements such as “We hypothesize that tumor tissues and normal tissues from the same organ will have different patterns of gene expression” are virtually useless — and reviewers don’t view them positively. Be more specific, perhaps saying, “We hypothesize that tumor tissue will display a gene expression profile showing elevated inflammatory responses.”

Area Grant applications may face looser criteria

If you’re applying for an Area Grant because you’re at an underserved institution, a lot of the criteria are loosened. In such cases, as a new investigator you could go with preliminary data for publications, although you ought to be able to say, “The data have been submitted for publication.” The NIH won’t allow you to put any manuscripts in, but if you can say honestly that the work has been submitted for publication, that reassures reviewers that you’re actually moving forward with the work. General Medical Studies is one of the institutes that sets aside a large portion of its funds for new investigators and is very supportive of them. Including a cover letter making it clear you want your proposal to be sponsored by GMS can definitely help you.

For the uninitiated, GMS funds basic research that’s not directly, specifically tied to a disease or an organ system that has its own institute, such as research that looks at the central underpinnings of biological function, but that doesn’t address cancer, diabetes, or heart disease. Each institute has its own philosophy and has its own portfolio of grants and its own attitude toward what is the most important thing it can do with its money — and GMS is dedicated to helping new investigators get started.

It’s a good idea to include a discussion of institutional-level collaborations in the Environment section of Area Grant applications. That is clearly the place to highlight unique aspects, like Historically Black University status. Individual-level collaborations should be highlighted in the Personal Statement.

Budget Justification section matters

Some applicants may be tempted to add details of their approach to the Budget Justification
section to boost their chances of getting all the funding they seek. While most reviewers do carefully review that section, they’re only making sure the budget is appropriate for the proposed experiments. You will be dinged if it’s perceived to be either too high or too low for the work proposed.

Simply put: Details of your experimental approach are inappropriate for this section; you can’t be sure all reviewers will read it or when they will read it. However, if your experimental approach justifies something that is unusually expensive, such as lots of animal costs for a transgenic study, then definitely do point that out in the budget section.

Note that your budget request is not supposed to factor in the overall impact score; it is in the Other category, discussed after a score is assigned. If the reviewers think your request is excessive, they will recommend cuts. That said, there can be so-called “budget envy” among some reviewers, especially if your salary structure looks high — as at a private company or national lab. It’s best to explain your salary structure in the Budget Justification if you think that might be an issue.

**Detail resources in Resources section**

Some applicants have wondered if Resources material should be included in or somewhere other than the newly named Research Strategy section. But keep in mind that there is, and always has been, a Resources page in the application. The new Environment discussion is supposed to go on that page. If there are key resources at your institution that uniquely enable your research, they should be referred to in the Approach section as appropriate, but the technical details should be expanded on under Resources.

**Military researchers similar to corporate applicants**

Finally, the only unique pitfall of military research is that the academic reviewers who examine your application often won’t understand the military system very well, just as they may not be familiar with how private grant-funded research works.

If you can collaborate with an academic, that will give you more credibility and ease some of the inappropriate discomfort that your reviewer might have over his or her unfamiliarity with research in the military setting.
Also, be very careful on your Human Subjects section that you’ve addressed the academic standards of human subjects research. Military personnel are considered to be a sensitive population historically, so make sure if you are using human subjects that you make the point that you comply with all NIH regulations. Basically, you’ll be judged on the quality of your research, but, particularly in your environment, you should run your proposal by a colleague who is not a military colleague. If you have inadvertently put in too much military jargon or have not addressed things that an academic would consider to be of concern, that other set of eyes will catch it for you.
Chapter II

Grant applications are complicated documents. It’s worth your time and effort to make sure you understand how to fill out the new form in a way that maximizes the chances your story will be heard.

Among the best advice NIH reviewers can offer you is this: With the shorter page limits, don’t take your old 25-page grant proposal and cut and paste to edit it down to 12 pages. It’s going to be choppy. It’s going to be incoherent. And there are not going to be good transitions. The reviewer will know what you did. It will not be an effective document. Rather, you should start from scratch, only cutting in already-written pieces that absolutely fit.

How well you navigate the technical aspects of a grant application can have a powerful bearing on the likelihood reviewers will get the information they need. Here are additional tips and tactics, provided directly to you by NIH reviewers. (You’ll find a nine-point grantsmanship “cheat sheet” in Appendix B.)

Use the “elevator speech”

The concept: You’re in an elevator with Bill Gates, who has $1 billion that he wants to invest in research. You have three minutes to convince him your idea is worth funding. Can you do it? That’s the level you want to get to on the first page of your application with your Specific Aims. Excite the reviewer about what you want to do. Remember, most reviewers make up their minds while reading the first page and then read the rest of the proposal looking for support of their impressions.

Tell a story: Making Reviewers care about your project

That’s exactly what you’re doing — trying to convince a reviewer to be emotionally involved in the research you propose to the point that the researcher wants to see your project funded, cares about the question you’re asking, and wants to see the results of your experiments — enough that he or she is willing to invest NIH’s resources in the research.

You need a compelling “plot”— a compelling scientific problem, something that you and the reviewer care about. That’s where Significance comes in. There should be some tension or
conflict, such as the knowledge gaps and the technical obstacles that have prevented other people from solving the problem you’re attacking.

That’s where Innovation comes in: You have a new idea for solving the conflict. There’s an action element here— the Technical Approach. Your research strategy is where you have to demonstrate your logical thought process, your tactics for executing the plan and your contingency plans if your first approach doesn’t work.

Finally, all good stories have a resolution: the boy and the girl get together or the bank is robbed and the burglar escapes. Your resolution is how the field will be changed as a result of your research and what future research will be enabled by your particular project. That’s Impact. All grant proposals should end with a short paragraph that goes over the impact: “At the end of the day, when this research is done, my field of research will be changed because when we know ‘this’ and ‘that,’ we can go on to the next thing,” whether it’s a clinical trial or the development of a new drug. (You’ll find more details on telling a compelling narrative in Appendix E.)

Know your audience. Know what the funding official is really looking for. Is your project basic science? A bench project? A translational research project? Are you a single investigator or part of a multi-disciplinary team? Do you need a clinical collaborator? Make sure you demonstrate how your research is responsive to the Request for Applications (RFA); if not, don’t waste your time, especially when applying for program announcement-based grants. For an R01, it is your idea, but you have to make a link between your idea and improving human health, because that is the mission of the NIH. The review criteria in general have become much more concerned with how much your project affects human health down the road.

Simplify

Many applicants are tempted to use small fonts, tight margins, and tiny figures and figure legends because of the lower page limit. Avoid that. There are times when a table or flow chart will say what you want to say in less space than the equivalent text, so use a chart or a table when it makes sense. The fewer pages you have, the simpler your story has to be. Focus on what is essential, but show your logic.
Have someone look over your application

Some consider this the most important reviewer’s tip of all. Get another set of eyes to read your proposal before it goes in. You should organize your time so you have a complete draft of everything, all 12 pages, a week to 10 days before you have to press the “send” button. Find someone — a colleague, a former student, someone in your department, a scientifically savvy significant other — to read your proposal.

Don’t rely on someone who has been working in your lab, doing the experiments you describe. You need someone who does not already know what’s in your head. A common grantsmanship error occurs when you know why Specific Aim 1 is connected to Specific Aim 2, but you haven’t stated it explicitly in your proposal, leaving the reviewer in the dark. An outside pair of eyes will catch that, ask you the key questions, and give you time to go back and write the transitional paragraphs you need to describe why and how those specific aims are connected.

Seek letters of support

If you’re a young investigator at an institution where you don’t yet have full institutional commitment, you must be frank in speaking to your department chair, saying “I’ve done my research, and I realize that with this new personal statement and resource page, the reviewers are going to be looking for commitment from you, my department chair, to my future. We would both benefit if I got the grant, so please write a supporting letter for me to go with my application saying what your level of commitment is to me as a young investigator.” Those supplemental supporting letters, which are not within the page limits, are a good place to go to get statements from people at your institution. They could even be colleagues you have worked with.

Use support letters to fill in gaps in your capabilities. For standard R01s, reviewers will weigh the importance of letters of support based on whether there’s a major gap in your capabilities that must be filled by a collaborator. In those cases, it’s insufficient to simply name a consultant. You need a strong, specific letter of support from that individual stating exactly what he or she will provide to the project — and demonstrating that party’s enthusiasm.

Although not technically required for collaborators who are co-investigators with Biosketches in the proposal, if there is little history of prior interaction, a letter of support is still valuable.
Proposals in response to calls for multi-disciplinary research are heavily dependent on strong letters of support from the participating parties, and letters of administrative support are needed if there will be a large commitment of resources at subcontracting institutions. Those letters are outside the application’s page limits.

Also, if you are entering a new field, having a letter from an established expert in that field is helpful. 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 establish your credibility. The letter should specify what support is being offered, and it must be plausible. Also, the letter must show sincere enthusiasm for your project. You can write it for the person, but don’t make all of your supporting letters look the same. Take the trouble to figure out what aspects of your proposal would be most interesting, and relevant, to each of your collaborators.

Focus on the “mechanistic” qualities of your proposal

Some applicants see “mechanism” as something of a Holy Grail at the NIH, while “phenomenon” is perceived to be frowned upon, regardless of novelty or import. While acknowledging that grants should be aimed at revealing mechanisms, those applicants feel that “one man’s mechanism is another man’s phenomenon” — and that “the only consistent rule for knowing you have a mechanism in your grant is that it has lots of dots, blots, and spots.” While it is true that “one man’s mechanism may be another woman’s phenomenon,” there are some characteristics of your project that can be used to increase the likelihood that your research will be seen as “mechanistic:”

- Your observations should be completely objective, and quantifiable. Observations that are qualitative and subject to interpretation by the reviewer can easily be dismissed as phenomena.
- You should be able to perturb the system and predict the response. The more quantitative the prediction, and the better the fit between your prediction and the experimental results, the more likely it is that you are close to revealing a mechanism.
- You should be able to postulate an upstream chain of events that leads to your observation — the mechanism by which the event occurs.
• You should be able to test your postulated mechanism by disrupting the chain of events, and losing the observed outcome.

The difference between the second point and the third and fourth is that the ability to perturb the system in predictable ways defines the system as amenable to quantitative study — as having a discoverable mechanism. The third and fourth points are the steps necessary to define the mechanism.

Another variant of the “mechanism” issue is the “hypothesis-driven” issue. It is easy to include the phrase, “We hypothesize that …” in your proposal. But be careful. It is useless, and even harmful, to say things like, “We hypothesize that treatment with Compound X will change the pattern of gene transcription in cell line Y.” To be mechanistically useful, the hypothesis must be falsifiable; it must be specific, and it must actually point to a mechanism. Instead, try, “We hypothesize that Compound X inhibits cell proliferation by inhibiting EGF tyrosine kinase activity, so that cells treated with EGF in the presence of Compound X will have a gene expression profile similar to that of control cells that have not been exposed to EGF.”

Use the progress report to detail previously published papers. When filling out a competitive renewal application, plan on giving a narrative summary of how each specific aim was achieved under the earlier funding, emphasizing an integrated, big-picture summary of the impact the research had. The actual list of publications attributable to the prior funding is still outside the page limit, so consider arranging the list of publications by specific aim identified by a subheading.

**Be stingy with supplemental information**

You can submit supplemental material, but it is strictly limited. Read the RFA carefully. Note that unpublished papers are no longer allowed in an appendix, period. And the new form’s rules stipulate that only published papers that are not freely available on the Internet should be included in an appendix.

In cases where you want to send your Special Research Opportunity (SRO) supplemental information after the submittal of the parent proposal but before the study section meets, that supplemental information usually is presented as a letter, which may or may not contain figures and tables. There is an informal two- to three-page limit. Note that reviewers are not
required to read supplemental data. Some do, some don’t. Supplemental data are really effective only if they demonstrate the solution of a key problem that threatened the feasibility of the proposal. For example, you needed to generate antibodies to your newly discovered protein so you could do pull-down experiments. You did not have an immunoprecipitating antibody when you submitted the proposal but now you do. Supplemental data showing specificity and the proper controls will help you in such a situation.

**Don’t hesitate to pitch long-term research**

You may have heard that five-year proposals are at a disadvantage compared with shorter grants. That’s not the case if the work clearly justifies a five-year time period. Clinical or pre-clinical trials get special consideration in that regard.

Use key words in your summary to get the best reviewer assignment. A summary, which used to be called the Abstract, is still required, and it still has its own separate page within the electronic application form package. And it is still outside the page limits. Not all reviewers read the summary, but the Center for Scientific Review uses it to assign your proposal to a specific study section and institute. So it’s important that you use the right key words in your summary to get the assignment you want.

**Don’t undervalue careful use of PMC numbers**

NIH policy states: “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 PMCID numbers along with the full reference. Note that copies of publicly available publications are not acceptable as appendix materials. In other words, if you are a co-author, and the work was funded by NIH after the Public Access Policy was implemented, you need to include the PMC.
Know the difference between “potential problems” and “high-risk aspects”

Potential problems obviously represent a risk to the success of your project. They might be trivial and easily solved — perhaps you will pool samples if you cannot get enough material for analysis from individual animals or patients. Or they might be major, posing a serious risk to successful completion of the project — perhaps no antibodies exist to your protein of interest and it’s not immunogenic in mice. By asking you to identify “high-risk aspects and management,” NIH is asking you to demonstrate the quality of your thinking about risk and your ability to develop alternate paths for achieving your goal.

Describe the background of your research when appropriate

Under the new arrangement, background needs to be divided between the two sections, Significance and Innovation. There needs to be some background, or context, to establish significance. But you also need to put your work in the context of what is already known to demonstrate innovation, and that is clearly “background” as well. The Significance section, then, should include background on why it’s important, and the Innovation section should include background on how your research builds on and extends what is currently known.
Chapter III

First Page of an Application

The new form is designed to streamline verbiage presented to reviewers, and the verbiage they offer you in response. If you focus on telling a simple story, there's plenty of room, even under the reduced page limit, to get your point across.

Here's how the first page of an application might look. The plot of your story is in the introductory paragraph, where you say why the reviewer should care about colon cancer as a fatal disease and about your efforts to detect it more accurately presymptomatically. The specific problem that you'll be addressing, in this hypothetical case, is that current approaches for measuring proteins in blood are relatively insensitive. The solution is new protein technology. All of that can be said in the first paragraph of your first page. (Look for details on telling a story in Appendix E.)

Your action plan is your specific aim or aims and, in this case, the specific aims do build on each other. So, in the Research Approach section, it is important to convince the reviewer that Specific Aim 1, identifying plasma proteins, will succeed, and that you have a track record of using the technology to accomplish it that you're planning to use. End the first page just as you end the entire proposal, with a statement that can be very explicit: “The end product will be in an accurate blood test.”

The Future Directions section includes the application of a biologic approach to bring new insight into related mechanisms. So you have both a short-term outcome and a longer-term outcome. You have a practical result and you have a theoretical result. And it all fits on one page.
Appendix A — Focus Shifts to ‘Impact’ of Work You Propose

The NIH short-form grant application, with its heightened emphasis on the overall impact of the research you’re proposing, may seem to make the application process more complex and the review process more random. Some of your colleagues who’ve tackled it, in fact, admit they’re not sure if they provided the information reviewers need to determine “impact.” One says he has no idea how the reviewers are going to judge his ability to highlight the impact of his proposed research.

The shortened form isn’t designed to make your work easier, of course. It’s designed to make reviewers’ work easier by streamlining the verbiage included in most applications and by encouraging reviewers to weigh that elusive concept of “impact” as a key determinant of a project’s fundability. The scientific fabulousness of a proposal isn’t what makes it worth spending public dollars on; rather, the proposal’s likelihood of actually being carried out and of changing the game, research-wise, is what matters.

But that can be a good thing if you make the effort to learn what can be learned about applying for grants using the short form. And, despite any ongoing confusion, there also are some very specific things you can do when using the new application to maximize the likelihood that reviewers will clearly see the overall impact of your research.

No template exists for highlighting Impact

There is not, it’s critical to note, a template for incorporating “overall impact“ into the new NIH applications. There’s no section called Overall Impact, for example, and there’s no incentive for you to simply add a paragraph labeled as such. Rather, the NIH Office of Extramural Research says, you need to describe “impact” clearly in whatever words are relevant to your project.

There’s a good reason for that. Rather than looking for a section devoted exclusively to impact in the new forms, reviewers want to see impact “bubbling up” through the entire application. If you put it in a box labeled Impact, reviewers may be tempted to cut and paste it into your review, and you won’t get any real feedback. The new form’s focus on impact, rather, is designed to improve the funding process by acknowledging that reviewers are humans and represent a variety of personalities and outlooks. You may have written a technically perfect
proposal under the old system, and reviewers could read it, yawn and say, “We already know how that works.” That’s what the NIH is trying to stop with the new proposals.

**Concept of ‘impact’ combines science with likelihood of success**

One experienced reviewer notes that impact in the new form is an integrated concept where it’s clear that your experiments address what you state in your Specific Aims section and that you’ll get useful information out of the study because the experiments are cleverly designed. Reviewers want to see that, not only are you addressing a timely and important problem, but that it actually can be accomplished in the period outlined with the resources requested — and that the information gleaned will be useful to the next generation of experiments or, potentially, will be translatable in the near term.

Reviewers, of course, sensed that impact was part of the focus of the form in the past. Now it’s clearly separated out. The problem is that impact for NIH reviewers may be something they can’t readily define, but know when they see it. One PI reports applying for a grant using the new form and finding the process to be challenging because of the new emphasis on impact. That PI’s sense is that both applicants and reviewers are in the middle of a learning phase. Applicants, in that PI’s view, are trying to clearly write their proposals to focus on impact, and reviewers are trying to sift through shorter applications and make determinations of impact.

Part of the problem, the PI reports, is that “impact” is fairly nebulous as far as concepts go. Reviewers, the PI feels, are much more comfortable with feasibility and scientific design issues, so it likely will take the next year, if not more, for both sides to reach some equilibrium.
Appendix B — Use These 9 Tips to Get the Most Out of Your Application

1. Start with a fresh sheet of paper. Don’t start with an old 25-page application that wasn’t funded and try to cut it down to 12 pages. Start over.

2. Pretend that you’ve got an hour to address an advanced biology class at an excellent high school or an especially bright group of college freshmen. What would you tell them to give the flavor of your research, its impact, and why they should get excited?

3. Don’t be obsessed with showing off how much you know, and don’t go into great experimental detail or include a lot of background on the history of your field.

4. Take the long view of “impact.” Reviewers want to know how the research you’re doing will change the field and translate into an impact in human health. So if you’re doing a basic study of, say, DNA repair enzymes, you need to say, “Even though this is basic research, it’s needed for new drug development.” Think that far ahead. Tell reviewers the ultimate utility of your research — even if it’s five years down the road.

5. Make your train of thought crystal clear. You know the logical connections in your head. You know why you’re doing a specific experiment. Don’t forget to tell the reviewers. Some of what they’re evaluating is your thought process — your summary of the significance of your research and your summary of its impact.

6. Don’t use words you don’t need. A 12-page form, as opposed to a 25-page form, means there’s a great deal of pressure on you to show your thought processes in a direct and architectural way. Show that you know what’s important and what’s superfluous.

7. Get a complete draft done at least 10 days before it’s due and find someone who’s not involved in the project — don’t use a post-doc in your lab — to check it out. That person can find the logical holes and can help you outline the impact.

8. Use the word “impact” as needed. It shows you paid attention to the new criteria for grants.
9. End your grant with a paragraph that says what the government gets at the end of the day if it funds your research. That’s exactly what “impact” is. The difference between significance and impact is, basically, that significance is whether what you’re doing is worth doing and impact is what the NIH gets after it’s funded you. You can be explicit: “At the conclusion of this research program, we will have identified [fill in the blank] and we will have determined [fill in the blank] and we will be on our way to developing [fill in the blank]. That’s impact.
Appendix C — NIH Document Offers Sample Questions, Case Studies to Explain ‘Impact’

The NIH is making an effort to explain what “impact” is and how you can make it clear in your application that your work has it. You should do so, the funding agency says, in the Specific Aims section of the application. Specifically, you should state concisely the goals of your proposed research and summarize the expected outcomes, including the impact that the results of the proposed research will exert on the research fields involved. But because reviewers are chosen largely because of their scientific and technical expertise and knowledge of the research field involved, you should be sure to present your project and address each review criterion in a manner that makes your work understandable to the reviewers.

There isn’t a fill-in-the-blanks way to do that. There used to be an overall score for “priority,” but now the overall score is called Impact, and it reflects the reviewer’s assessment of the likelihood your project will exert a sustained, powerful influence on the research fields involved. Reviewers evaluate each review criterion and weigh each one as appropriate for the proposed research when determining overall impact — the compilation of the evaluation of the review criteria. As reviewers assess overall impact, they take into account the individual criteria and provide an overall evaluation. There’s still a subcategory of review called Significance, which is the source of much of the confusion over the new focus on “impact.”

In a recently released document titled Overall Impact Vs. Significance, the NIH clears up, for reviewers, the confusion between the two. Here’s a transcript:

Since the release and implementation of NOT-OD-09-025, “Enhancing Peer Review: The NIH Announces Enhanced Review Criteria for Evaluation of Research Applications Received for Potential FY 2010 Funding,” there has been some confusion regarding the distinction between Significance and Overall Impact. In response, the NIH Office of Extramural Research convened a working group consisting of NIH review and program staff to develop additional guidance on this issue.
Definitions From NOT-OD-09-025

- **Significance:** Does the project address an important problem or critical barrier to progress in the field? 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 preventive 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 fields involved, in consideration of the 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.
- 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 core review criteria that are scored individually and the additional review criteria which are not scored individually.
- 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).
  - 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.

Significance

- Significance is evaluated and scored independently of the evaluation and scoring of investigators, 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. For example, autism is a significant field of study, but not all studies (projects) of autism are significant.
- 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.

- 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

Q1: I’ve read the definitions of Significance and Overall Impact, but the two still seem rather similar. Can you provide some additional guidance?

A: Significance is a stand-alone assessment of the project’s goals in the context of the relevant field, and to a large extent assumes that the investigators, approach, and environment are adequate to allow for successful completion of the aims of the project even if later discussion of each of these review criteria will identify problems. When reviewers assess the Overall Impact of an application, they are expected to take into account the five core review criteria (significance, investigators, innovation, approach, and environment) and the additional review criteria to judge the potential of the project to exert a sustained, powerful influence on the field.

Q2: Overall Impact uses the same scale definitions as the five core criteria; how is it different from a sixth review criterion?

A: The Overall Impact score is a synthesis that takes into consideration all of the five core review criteria (significance, investigators, innovation, approach, and environment) as well as all of the applicable additional review criteria.

Q3: When determining the Overall Impact score, should it equal the arithmetic mean of the scores for the five core review criteria?

A: Not necessarily. The Overall Impact score considers all five core review criteria as well as all applicable additional review criteria. In addition, an application does not need to be strong in all five core review criteria to be judged likely to have a major scientific impact. Therefore, it is possible for one or more review criteria to overshadow the other review criteria, thus driving the Overall Impact score up or down. Please remember that there is no formula to derive the overall impact/priority score from the individual criterion scores. Reviewers are instructed to weigh the different criteria as appropriate for each application in deriving the Overall Impact score.
Q4: Is it possible to have an application receive a moderate score for Significance yet receive a very strong Overall Impact score?

A: One can envision such scenarios. For example, a talented investigator in a very strong environment proposes a highly innovative and very sound approach to address a generally important problem (e.g., breast cancer). However, the proposed project will be relevant to only a narrow area within the larger field of breast cancer research, thus reducing its Significance. Nevertheless, the Overall Impact score could still be strong since the strengths of the project in the other core review criteria give this work the potential to have a sustained, powerful influence on that part of this important field.

Q5: Is it possible to have an application receive a very strong score for Significance yet receive a moderate to low Overall Impact score?

A: Yes. The Overall Impact score synthesizes all five core review criteria as well as all applicable additional review criteria. Thus, while the significance of the project is very strong, the investigator may lack key credentials, the innovation might be minimal, the approach might be problematic, and the environment might not offer adequate support for the project.

Q6: Is it possible for an application with numerous weaknesses in Approach to receive a very strong Overall Impact score?

A: Yes. No single review criterion (e.g., Approach) alone determines the Overall Impact score. A project may have numerous minor weaknesses that affect the score for Approach, yet still have a very strong Overall Impact score if the application is exceptionally strong in the other review criteria and the quality of the team and environment lend confidence that the project will have a major overall impact on the field. “Minor weaknesses” are defined as “addressable weaknesses that do not substantially lessen overall impact.”

Q7: Aren’t projects that address diseases of large public health importance (e.g., heart disease, cancer, autism, or dementia) inherently significant? Should they automatically receive high marks for Significance?

A: Not necessarily. The Significance score reflects whether a project addresses an important problem or critical barrier to progress within the field. For example, while a project may
generally address a devastating disease with high prevalence, the specific problem addressed in the project may be only tangentially related to the disease, the problem may not be very important for patients with the disease, the proposed work may duplicate already-published reports, or the expected results may be unlikely to substantially change knowledge, concepts, and/or practice in the field.

Q8: Conversely, are projects that address rare diseases, diseases with modest burden, or highly focused research questions inherently less significant?

A: No. Work on rare diseases, highly prevalent diseases with modest burden, and highly focused research questions can still be extremely important. Reviewers should judge whether the proposed goals and aims address an important problem or critical barrier to progress in the field, whether the proposed work will improve scientific knowledge, technical capability, and/or clinical practice in the field, or if the project will change the concepts, methods, technologies, treatments, services, or preventive interventions that drive the field.

Q9: The verbal descriptions for high, medium, and low overall impact in the Scoring System and Procedures document indicate that applications with high Overall Impact (i.e., a score of 1-3) have “no to some minor weaknesses.” Is this is always the case?

A: Not necessarily. The verbal descriptors and additional guidance on Strengths/Weaknesses are offered only in an effort to provide continuity in scoring between study sections. However, reviewers must not just “count” strengths and weaknesses to arrive at the final Overall Impact score. Remember that the Overall Impact score represents a synthesis of all of the review criteria and what may be a moderate weakness to one reviewer may only be a very minor weakness to another reviewer. For example, a very strong investigator in a very strong environment is addressing an extremely important problem. The approach is very innovative and could revolutionize the field. However, because the approach is so new and has not been tried before, it is not guaranteed that the project’s goals will be met, and some reviewers see this as a weakness. However, in the end, the study section concludes that the potential rewards far outweigh the risk(s) associated with the approach and that the application deserves a high Overall Impact score.
Q10: **The definitions of Overall Impact and Significance refer to a project’s ability to exert a powerful influence on or address an important problem within the research field(s) involved. I thought the goal of the NIH is to improve public health. What’s the difference between improving public health and addressing an important problem within a research field?**

A: The mission of the NIH is to support research in pursuit of knowledge about the biology and behavior of living systems and to apply that knowledge to extend the healthy life and reduce the burdens of illness and disability. To accomplish this mission, the NIH supports biomedical and behavioral research representing a wide array of research fields as well as tool development, clinical trials, and other projects in support of the biomedical research enterprise. In an effort to fairly evaluate scientific and technical merit through the peer review system of a broad range of applications (those that seek cures, not only for diabetes, heart disease, and autism, but also for the lesser recognized orphan diseases and those that are basic biomedical questions), it is important that Significance and Overall Impact be evaluated within the context of the research field involved. NIH program staff and Institute leadership will evaluate each project’s relevance to their Institute mission in making funding decisions.

Q11: **What should be considered in assigning the Overall Impact score for applications submitted for RFAs and other special initiatives?**

A: Funding Opportunity Announcements (FOAs) for IC-specific RFAs and targeted trans-NIH initiatives (e.g., Roadmap or Common Fund), including infrastructure- and capacity-building programs, may include additional FOA-specific review criteria in addition to the five core review criteria and the standard NIH additional review criteria (human subjects, animal welfare, renewal, resubmission, biohazards). The Overall Impact score for applications submitted for these initiatives should reflect the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the five core review criteria as well as all additional review criteria (as applicable for the project proposed) and the likelihood that the project will advance the stated goals and objectives of the program as articulated in the FOA.
Q12: What should be considered in the Overall Impact score for fellowship (F) applications?

A: For fellowship applications (Fs), the overall impact score should reflect the reviewers’ assessment of the likelihood that the fellowship will enhance the candidate’s potential for, and commitment to, a productive independent scientific career in a health-related field, in consideration of the five scored review criteria (i.e., Fellowship Applicant, Sponsors/Collaborators/Consultants, Research Training Plan, Training Potential, and Institutional Environment & Commitment to Training) as well as all applicable additional review criteria.

Q13: What should be considered in the Overall Impact score for career development (K) applications?

A: For career development award applications (Ks), the overall impact score reflects the reviewers’ assessment of the likelihood for the candidate to maintain a strong research program, in consideration of the five scored review criteria (i.e., Candidate, Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring, Research Plan, Mentor(s)/Consultant(s)/Collaborator(s), Environment, and Institutional Commitment to the Candidate) as well as all applicable additional review criteria.

Q14: What should be considered in the Overall Impact score for institutional training grant (T) applications?

A: For institutional training grant applications (Ts), reviewers are asked to provide an overall impact score to reflect their assessment of the likelihood for the proposed training program to promote the training of pre- and post-doctoral fellows in biomedical, behavioral, and clinical research, in consideration of the five scored review criteria (i.e., Training Program and Environment, Training Program Director/Principal Investigator, Preceptors/Mentors, Trainees, and Training Period) as well as all applicable additional review criteria.
Q15: What should be considered in the Overall Impact score for shared instrumentation (S10) applications?

A: For shared instrumentation applications (S10s), the overall impact/benefit score reflects the reviewers’ assessment of the potential benefit of the instrument requested for the overall research community and on NIH-funded research in consideration of the five scored review criteria (i.e., Justification of Need, Technical Expertise, Research Projects, Administration, Institutional Commitment) as well as all applicable additional review criteria.
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: A Novel Method of Viral Vector-Mediated siRNA Delivery

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 illnesses. 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 illnesses. 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.

Scenariio 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 illnesses 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: Disruption of a Well-Known Signal Transduction Pathway in Mice

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 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 developing a new drug treatment for breast cancer.
Case Study #3: A Chemical Agent in Animal Model

An application proposes to develop and test an antidote for a chemical agent in 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 of 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 mortality. The reviewers might note the highly qualified investigators, flawless methods, and 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 effects, 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 the human condition. – Low Overall Impact
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