

VIEWPOINT

To grant you an edge: Part 1. General strategies for writing competitive biomedical research proposals

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In academic biomedical research, whether you are performing pre/postdoctoral scientific training or directing an independent laboratory, chances are you will be expected to develop and submit competitive grant applications. The latter is defined here as proposals that receive enthusiastic comments and scores in peer review, including enough funded applications to support the research activities of the investigator or laboratory. The importance of submitting competitive grant applications has been discussed in a recent Viewpoint in this journal (1). The most obvious and practical reason, of course, is to provide revenue to pay for the personnel and non-personnel-related costs associated with achieving your laboratory's original research and scientific training missions (Fig. 1). This funding is referred to as the "direct costs" component of a grant award. Most research grants also include additional funds ("indirect costs") for the academic institution sponsoring the research to help offset the infrastructure-related overhead costs of supporting the proposed research activities, including facilities upkeep (laboratory and office temperature control, lighting, power for equipment such as freezers, etc.) and renovations, and the administrative space and workforce necessary to prepare and submit grant applications, oversee the financial aspects of funded proposals, and provide the necessary research-related regulatory oversight.

There are, however, other important reasons to engage in the process of competitive grant writing beyond these monetary considerations. From a career advancement perspective, your record of obtaining grant funding, particularly extramural funding (i.e., from sources outside of your institution), is a key metric considered during the annual evaluation of your academic research performance; during promotion and tenure reviews; when being considered for prestigious service appointments (e.g., a reviewer for national grant funding agencies); or when competing for new academic faculty or administrative research positions (1–3) (Fig. 1). Moreover, your success in submitting competitive extramural grant applications is viewed by professional peers as validation of the novelty and biological/biomedical significance of your scientific ideas and the rigor and innovation of your experimental approaches (1). Less appreciated, perhaps, is the fact that developing competitive grant applications often provides a useful structure, timeline (urgency), and creative process for

producing your best science (1). Indeed, the exacting nature of the grant writing process with the looming expectation of tough scrutiny by peer investigators represents a singularly unique opportunity for ongoing intellectual growth and critical scientific development that you might not otherwise experience if left to the less demanding setting of day-to-day research planning in the absence of a proposal deadline and subsequent peer review. From this perspective, the competitive nature of grant writing typically brings out our best efforts and end products (Fig. 1).

For all the abovementioned reasons (albeit primarily the need to obtain funding), academic research institutions expect you to submit competitive grant applications on a regular basis (1). Although an effort- and time-requiring process, regularly developing and submitting grant applications per se is a task that most principal investigators and their research laboratories can and do accomplish. Consistently submitting grant applications that are competitive for funding is an altogether different matter.

Our laboratory has been continuously funded by extramural grant awards for the past 36 years, mainly by the National Institutes of Health (NIH), the main federal agency responsible for supporting biomedical research in the United States. During that period, we have received as principal investigators (PIs) over 90 major grant awards totaling almost \$50 M in direct costs to support our original research projects and the scientific training of undergraduate and graduate students, postdoctoral fellows, and junior research faculty. Maintaining extramural research funding for a large and productive biomedical science laboratory over such an extended period is no small task. Success requires constant dedicated effort, but also an unabating willingness to better understand, explore, and routinely apply the "best practices" of effective grant writing. Complementing the lessons learned from our own grant writing efforts, I also have had the opportunity to serve on numerous grant review panels spanning the entire continuum of applications from funding mechanisms aimed at providing general laboratory research project support to proposals targeting different levels of research career development training. These collective grant writing and reviewing activities have provided valuable insight from which to view the process of effective proposal construction.

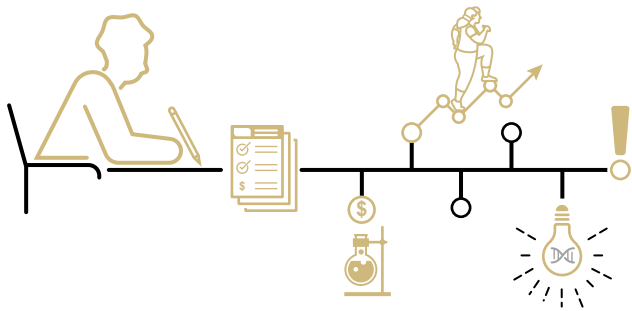


Figure 1. The importance of submitting competitive grant applications. Among the most compelling reasons for developing competitive grant applications are 1) funding your original research and/or scientific training activities; 2) optimal career advancement (record of research performance); and 3) producing your best scientific ideas. Illustration by Steve Graepel.

In this 3-part Viewpoint (4–6), I share selective thoughts for competitive grant writing in the biomedical sciences. Because the review criteria for grant applications depend on the funding mechanism in question (e.g., research project support versus career development), in Part 1 of the Viewpoint (4), I will focus on general strategies that may be helpful in most if not all biomedical grant writing scenarios. In Part 2 (5), I will share impressions and tactical tips for developing specific aspects of biomedical research proposals, whereas in Part 3 (6), I discuss writing competitive applications for research career development awards (predoctoral and postdoctoral individual fellowship proposals and applications to provide support for junior faculty investigators).

I acknowledge up front that much information already exists on best practices for grant writing in biology and the biomedical sciences. Guidelines are available from experienced investigators, consensus groups commissioned by scientific organizations, and staff working in grant funding agencies, and provide broad, invaluable coverage of the topic (7–15). The information shared in the present Viewpoint is not intended to serve as a comprehensive, step-by-step procedure for how to write a grant proposal or as a substitute for these alternative sources of expert advice. Rather, this commentary should be viewed as selective “insider notes” based on my extensive personal experience in directing an extramurally funded biomedical research program and serving on grant peer review committees. My perspectives are primarily intended for early career stage investigators (graduate students to junior faculty), although some of the suggestions also may resonate with established scientists directing independent research laboratories.

■ UNDERSTAND THE PEER REVIEW PROCESS —AND PEER REVIEWERS

Before beginning the process of developing a competitive grant application, it is advantageous to understand the peer-review process used by the funding agency from which you seek research support. Those organizations typically will provide an overview, if not a detailed description, of the structure and procedures involved. You will find certain commonalities among most if not all agencies. For example, your

proposal likely will be critiqued by three or four reviewers. Learn as much as you can about the overall peer-review process. However, at the core of any system will be those few reviewers assigned to your application. In the following sections, I share some impressions of the peer-review process of biomedical research proposals. I will focus on that small, but highly influential group of peer investigators charged with evaluating your application and how to most effectively interface with them to produce the best outcome possible.

This Is a Partnership

No, I am not referring to a collaboration with a colleague to develop a grant application, but rather a partnership between you and the reviewers of your grant proposal. It may seem paradoxical, but when you submit a grant application you are in essence entering into a mandatory working relationship with a small group of anonymous peer reviewers. The reviewers are representing the interests of the funding agency and the taxpayers, businesses, foundations, and/or private donors who have contributed to the agency’s pool of grant funds. The contributing parties hold the unspoken expectation that those funds will be distributed (invested) in the highest impact, most societally meaningful research possible. The reviewers are being asked to evaluate your proposal for scientific merit and their assessments are used by the grant organization to identify specific applications for funding consideration. Most reviewers take their responsibilities seriously and devote significant time and effort to the grant evaluation process. These efforts are deserving of your acknowledgment, respect, and utmost professionalism. Although administrators in the grant funding agency can be helpful in identifying organizational research priorities that may be a good fit for your scientific interests, the grant reviewers are the individuals that evaluate your proposal for scientific impact. Your application will not be seriously considered for funding by the grant agency without a strong scientific merit score from those reviewers. The essential point here is that the outcome of your grant submission will be determined not only by your best individual efforts to create a strong competitive proposal but also by the success of your partnership with the reviewers.

Develop “Reviewer Empathy”

Empathy may be defined as the capacity to understand what another person is experiencing from their point of view. Empathy is imagining yourself in someone else’s place. In this case, the reviewer’s place. To do so, it is useful to appreciate some basic facts about that select group of individuals. Most grant reviewers in the biomedical sciences are mid-career or senior investigators who work at research-intensive academic institutions. The majority are directing independent research laboratories. While reviewing your application, they are trying to write their own competitive grant proposals to keep their laboratories funded. The reviewers also are supervising research staff, mentoring students and postdoctoral trainees, teaching, and performing a wide range of professional service activities. Many have extensive family responsibilities. Physician-scientist reviewers may have a busy schedule of patient clinics. The overall obligations

typically are so great that the average reviewer has difficulty even keeping up with the basic duties of their primary faculty appointment. Superimposed on these existing demands is the reviewer's regular voluntary participation in the grant review group to which your application (and dozens of others) has been assigned. This is the setting in which your proposal will be evaluated: a beyond-busy, overloaded, overworked scientist who must somehow pause work on their other onerous commitments to create the time and focused energy to review your grant proposal and maybe 10 additional 200+ page, single-spaced grant applications—a task that may take an entire day (or more) per proposal. Many grant reviewers repeat this process up to three times per year for multiple consecutive years as part of their agreement to serve. Reviewing extramural research proposals is a time- and effort-intensive, physically-mentally-emotionally stressful, energy-sapping (often exhausting) situation that, as the grant writer, demands your full, unqualified empathy if you seek the best outcome for your application (Fig. 2).

Operationalize That Empathy

Developing empathy for your grant reviewers is an essential first step but operationalizing that empathy—translating it to your grant writing—is even more important to properly support your end of the partnership. In this context, your major responsibility is to facilitate reviewer's understanding of the key concepts and essential details of the grant plan while minimizing the burden of the evaluation process. Try to make that process as time-efficient and energy-sparing as possible for reviewers to find, interpret, and synthesize the critical information that will most strongly influence their opinion of the scientific merit of your grant application. To help accomplish this, present that information in the most well-organized, straightforward, and uncluttered manner possible (Fig. 2). Do not make reviewers work any harder than necessary to assess the content you are attempting to share. To err on the safe side, assume a priori that by the time the reviewer is ready to evaluate your proposal they already are somewhat burned out and perhaps a bit irritable, privately lamenting the enormous amount of time the process is requiring (as they see their other work piling up), and operating under the stark realization that they have several more applications to review to meet their fast-approaching submission deadline for all their assigned

proposals. Help them to identify the strengths of your application and become highly enthusiastic about the proposed science while exerting the least amount of effort possible in reaching that favorable conclusion.

Tips for Being a Good “Partner”

Okay, message received—as the grant writer, you need to be part of the solution, not part of the problem. So, how can you help? How can you be a “good partner”? One key is to present the information in the most reviewer-friendly manner possible. Here are a few basic tips, including format-related recommendations, to get the ball rolling. I will share other types of strategies for effective grant writing in the ensuing sections of the Viewpoint.

Write precisely.

Make clearly interpretable statements, defined here as statements that have only one meaning. If the statement might be interpreted by a reviewer another way, rewrite the sentence in question until it meets the standard of having only one possible interpretation. The same principle is important when explaining longer, more nuanced concepts, and when describing the components of illustrations. Write with precision: every word, line, paragraph, and section of the application.

Emphasize simplicity.

Focus on three important “S’s” of effective grant writing: straightforward, simple, and succinct. In doing so, avoid:

- meandering, nonlinear narratives within sections of the text;
- overly complex wording (use simple words and phrases);
- long (“run-on”) sentences;
- use of vague, informal, or slang terms (“we ran several experiments” vs. “we conducted or performed several experiments”);
- discipline-specific terminology (reviewers may work in a different area of biomedical research); and
- excessive use of abbreviations (reserve use for longer, frequently used terms).

All these writing behaviors increase the reviewers' cognitive burden when trying to understand exactly what you are describing. Adding to a reviewer's already substantial effort comes with a consequent risk of annoyance, frustration, and crankiness toward your proposal, and likely a reduction in your merit score.

Enrich readability.

Enrich the readability of the information presented by diversifying the visual appearance of the text in part by varying style and formatting approaches (Fig. 3).

- I. *Employ generous spacing:* Integrate spacing into your initial drafting of the narrative text, tables, and figures, then protect it from your own subsequent space-saving edits. Densely presented text both within a page frame and page to page can contribute significantly to “reviewer fatigue.” Generous use of space positively influences reviewer mood, attitude, and interest while they attempt to cover

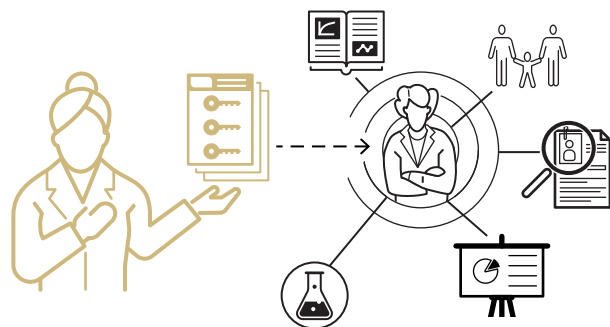


Figure 2. Develop and operationalize reviewer empathy. The grant applicant (*left*) should form an empathetic “partnership” with the peer reviewers of their research proposal (*right*) that recognizes the reviewers’ many other professional and personal responsibilities. Illustration by Steve Graepel.

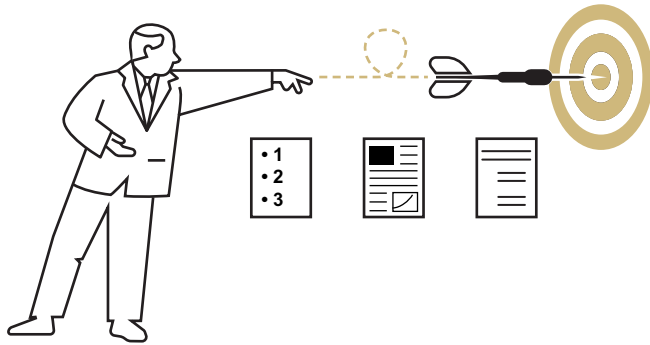


Figure 3. Aim to enhance the readability of your proposal. Tips for being a good partner to the reviewers of your grant application include enhancing the readability of your proposal by 1) using short paragraphs and bullet formatting; 2) employing generous spacing; 3) varying your fonts; and 4) emphasizing schematic figure-based images. Illustration by Steve Graepel.

what can be an overwhelming amount of content. Create ample spacing and stubbornly defend it.

- II. *Use short paragraphs:* Structure your content in short paragraphs with spaces between those paragraphs. A page of text built with properly spaced, short paragraphs is much easier to work through and more appealing to read than long paragraphs with few or no breaks. This approach will serve to lighten the load (and brighten the mood) of your reviewers. Employ frequent use of sub-headings in conjunction with this short section format strategy for purposes of organizing subtopics and helping reviewers follow the distinctive parts of the overall story you are attempting to present.
- III. *Intersperse “bullet” type formatting:* When presenting a list of items within a sentence or paragraph, consider using bullets or some equivalent format to vary the appearance of the wording, describing the information as a vertical list rather than packing the items end-to-end in a long, continuously winding, multiple-line section of text. Although this approach may not always be possible (e.g., because of space restrictions), use bullet-type formatting periodically to diversify the text to enhance readability. Again, any source of variation in the typography of the narrative pages of your grant application is easier on the eyes (and psyche) of reviewers than long blocks of single-spaced standard text.
- IV. *Vary your fonts:* Another tool for diversifying the appearance of your narrative text is to vary font features using italics and bolding (individually or in combination) of specific terms to create a subheading or to highlight a term or passage. Avoid “underlining” in general and particularly for more than a word or two in sequence because underlined text is more difficult to read than regular text. In general, you should avoid too frequent use of any font feature, as this can desensitize readers to their use and the highlighted wording will lose some of the intended distinctiveness.
- V. *Emphasize schematic images:* Use schematic images to provide visual support for your descriptive text when

explaining complicated events, including mechanistic processes, complex physiological interactions, integrated working hypotheses, and organizational features (e.g., study designs; procedural workflow; experimental groups and conditions; and/or study timelines). The schematic images should be well organized, uncluttered (limited components populating the visual field), and clearly depict how the events are connected in sequence and direction. In competitive grant applications, “a picture” is indeed often “worth a thousand words.”

Before you ask, yes, the merit of the proposed science or research training is the single most important component of a grant proposal. And, yes, the most well-organized, clear, reader-friendly format will not overcome fundamental deficiencies in a research project or training plan. That said, reviewers readily note and appreciate a well-written grant application, and that distinction will give you a competitive edge against similarly meritorious research or training plans that are much more difficult to read and understand. Ultimately, like a compelling classroom lecture or thoughtfully crafted research seminar, it comes down to being an effective teacher. Walk the reviewers through your research pitch, step-by-step, in the clearest and most effort-saving fashion possible (Fig. 3). Consistently following this process will pay major dividends to you and your laboratory.

Think like a Reviewer

Research grant applications begin with scientific curiosity and excitement about an idea stemming from the creative thinking of the principal investigator (PI) and other members of the investigative team. The idea is translated into a research proposal via an organic process cultivated by the grant writer and colleagues, driven by the collective intellectual energy of the group. To endure (and complete) the arduous process of successful proposal development, the PI and other parties involved must believe in the merit of the project. After all, if the grant writers are not excited about the ideas and potential impact of the proposed research, how could reviewers be enthusiastic? The grant writers must be the primary source of insight and stimulation for constructing a competitive grant application.

That fundamental point conceded, an effective proposal development process should not be governed strictly by what makes sense to you, what you feel is intriguing, or about how you think everything works or is connected. Rather, with those sentiments serving as an initial foundation, you must build a narrative that will resonate just as strongly with external reviewers as it does with you and your colleagues. To produce the strongest possible grant application, you need to step outside the inherently limited scope of your own impressions about what you are proposing and into the mindset of the reviewer (Fig. 4). This is one of the most important strategies for developing competitive research grant applications: to think like an objective peer reviewer rather than an understandably biased, somewhat nearsighted proposal writer (we all are). Not placing adequate emphasis on thinking like an external reviewer is a common mistake, particularly by early career-stage PIs. Although it may sound odd, even a bit harsh and offensive to the ears of the industrious grant writer, at the most practical level of the extramural funding enterprise it

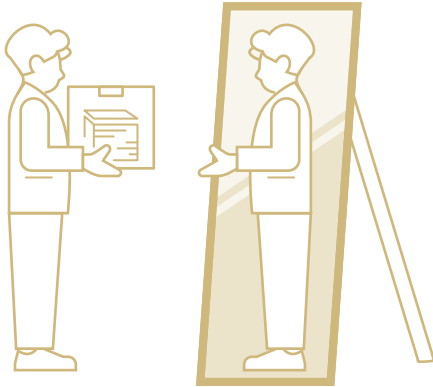


Figure 4. Think like a reviewer and let them know that “you know.” The grant writer (*left*) should step into the mindset of the reviewers (*right*), anticipate their questions and concerns, and develop the proposal content accordingly. Ensure that reviewers understand that you are aware of all relevant issues and potential problems with the proposed research. Illustration by Steve Graepel.

does not matter what ideas or experimental approaches strike you as worthy, only what is likely to captivate reviewers.

One approach to incorporating the reviewer’s mindset into your proposal writing process is to develop the initial draft of a sentence, paragraph, or section as the grant writer, then try to self-edit the newly written text from the impartial, detached perspective of a grant reviewer. That is, how might a naïve reader view what you have just stated? During that self-editing process, you should consider not only how intriguing the ideas presented will be perceived by an outside reviewer with limited background on the topic, but also what questions, concerns, and recommendations for change your statements may evoke (Fig. 4). To become an effective grant writer, you must develop an ability to play the “Devil’s advocate”—to anticipate reviewer responses to the information being presented. What are the known or possible experimental limitations of what you are proposing? As perceived weaknesses in the proposal accumulate, the reviewer’s enthusiasm for the application (and, as a result, your merit score) usually declines, with the magnitude of decline being proportional to the number and severity of the concerns. In the end, a noteworthy list of discerned weaknesses, even if only a few are considered significant (vs. “minor”), can stockpile and reduce your score just enough to drop below the funding line (“death by a thousand cuts,” as it were). As such, an essential goal of effective grant writing should always be to identify possible weaknesses (not just in your eyes, but in the eyes of an impartial reviewer) during proposal development so that those potential problems are eliminated before the application is submitted. Tactically speaking, the objective is to completely preempt possible criticisms and, if not, to at least minimize the functional impact of the weakness on your overall merit score by making targeted changes to the project plan during the grant writing process. Specific approaches for reducing potential reviewer criticisms are discussed in the sections below.

Make Sure They Know That You Know

One of the more effective strategies for intercepting criticisms before they can be made is to let reviewers know

that you are aware of the relevant issues and potential concerns of the proposed research (Fig. 4). This effort includes noting the experimental approaches that you considered and why certain options were selected, whereas others were dismissed. Follow the process with all the important choices you make throughout the various sections of the text. In my experience, the failure to understand and execute this strategy is one of the most common (and costly) mistakes made by grant writers, early stage investigators included. Many proposal writers assume that the rationale for the choices they make during development of the grant plan—from selection of aims and formulation of the working hypotheses to the study design, experimental procedures, and statistical analyses—will be innately understood (and approved) by reviewers. These assumptions are made even though many if not most reviewers lack expertise in the proposed topic and subtleties of the research being described; indeed, some reviewers assigned to your application may work in a completely different field. Parenthetically, this is the reason why grant agency guidelines often emphasize writing biomedical research proposals for a nonexpert reviewer.

My advice is to assume that the reviewer will not understand why you are proposing what you are proposing—the potentially problematic issues, the alternative approaches you considered, and why you made the choices you made. That is the only safe assumption you should be making. Instead of expecting reviewers to read your mind, you need to be the mind-reader. As you develop the application you will encounter dozens of questions that will require thoughtful consideration and well-reasoned decision-making. Stop and weigh the pros and cons of each choice carefully. Consult other members of your investigative team (or outside experts) as is helpful. For each issue, consider which option represents the most rigorous, definitive approach scientifically and, therefore, can be most strongly defended to preempt serious reviewer criticisms. Even if a reviewer does not agree with your decisions in every instance, explaining your choices will be acknowledged (i.e., the reviewer will know that you know) and the impact of the criticism on your merit score likely will be smaller than would otherwise be the case.

GENERAL RECOMMENDATIONS FOR EFFECTIVE PROPOSAL WRITING

Use Your (Limited) Space Wisely!

Not enough space.

Grant applications have strictly enforced, section-specific page limitations. The challenge these restrictions pose for the grant writer stems from the common expectation of reviewers that the proposal writer will provide all the necessary details required for a thorough critique of the research idea and experimental plan within the page-limited sections in question. That is, reviewers expect to see a comprehensive discussion of the published literature related to the topic; a detailed description of the animals or human subjects (e.g., inclusion/exclusion criteria); the specifics of the proposed experimental approach (study design, models, protocols, measurements); exact procedures for the statistical analyses of the results; and so on. Although the desire to have all this information presented by the applicant is understandable, it is

simply not feasible. Parenthetically, it is ironic in that reviewers are first and foremost grant writers themselves and face the same difficulties in meeting reviewer expectations when developing their own proposals. In any case, this situation leaves grant writers, especially early career investigators, contemplating how to provide reviewers with the seemingly overwhelming amount of information they demand within the available space. Clearly, choices need to be made—what to leave in; what to leave out (Fig. 5). It is a dilemma we all face in developing competitive grant applications.

Priorities.

In approaching this universal grant writing challenge, certain information clearly must be prioritized. For example, sufficient information from findings in the published literature, as well as unpublished (“preliminary”) results collected by members of the investigative team, must be presented to establish a strong scientific premise for the proposed research, defined as the knowledge upon which you are basing your hypotheses and aims. Similarly, the details necessary to evaluate the appropriateness of the experimental methods must be provided. These requirements are obvious. Rather, the key questions become how much detail to provide and how to provide that detail in the most space-efficient manner. In other words, how do you use your limited space most effectively?

Describing methodology.

Describing methodology is a prime example of a section that requires efficient space utilization because it represents such a highly page-consuming component of most research applications. One strategy to consider for providing this information in a space-saving manner is to present a “fundamentals-only” description of the experimental models, protocols, measurements, and analyses proposed, using references from your published original research articles to provide access to the details of those methods. Although some reviewers may be annoyed at the inconvenience of having to look up some specific point of interest, in fairness, they cannot argue the fact that you have provided access to that information via your referenced citations. So, in terms of what to

“leave out,” keeping your descriptions of methods (particularly measurements) brief by citing the laboratory’s more detailed explanations of those procedures in a published paper represents an important space management tool.

Justifying scientific choices.

In contrast, as discussed in the preceding section, there will be numerous situations during proposal development when you are forced to consider different experimental options and decide on approach a, b, or c. In my opinion, this is a good example of “what to leave in.” I strongly recommend prioritizing your space to provide justification for these choices because this is often the information that reviewers demand: why did you choose that approach and not the other? Unlike details related to methods, however, usually, there is no reference to cite to describe your rationale—no mechanism for reviewers to find the answer via their own agency. Rather, dedicated space must be allocated for this information within the page limitations of the methods section. Again, failing to justify your choices in developing a research plan is a common error in grant writing and one that usually can be avoided by prioritizing space as needed to explain your thinking to reviewers.

Final considerations for effective space management.

Simply being mindful of the page limitations as you develop the key sections of the proposal provides a useful ongoing reminder to write simply and succinctly and to continue to apply good practices for space use at every opportunity. You also may consider developing a “page budget” when planning coverage of the various sections or subsections of the application. Finally, make sure that all the information being presented is essential for reviewers to evaluate the proposed research, particularly the scientific aims. Avoid “rabbit holes” in which background on biological processes, including potential mechanisms of action, is described when those processes are not actually being investigated as part of the experimental plan. The latter may happen inadvertently when attempting to provide foundation to help reviewers understand the broader background of the topic. The overarching point here is to develop effective space utilization techniques and incorporate those tactics into your everyday grant writing process rather than writing without structure or strategy, ending up well over your space limit, and having to make draconian cuts or, even worse, completely rewrite sections of the grant application.

There Are Many Instructions, but Few If Any Rules!

Many instructions.

When developing a biomedical grant application, there are numerous instructions to heed. Careful review of those instructions before starting the writing process is essential to ensure that you understand what information is required, in what order, using what format(s), etc. Failure to read, understand, and follow the instructions issued by the grant agency may result, at best, in you not providing program officials and/or reviewers with all the information needed to process and evaluate your proposal. At worst, not following these guidelines may cause your application to be flagged and administratively withdrawn by the grant organization for some violation and returned without review. The

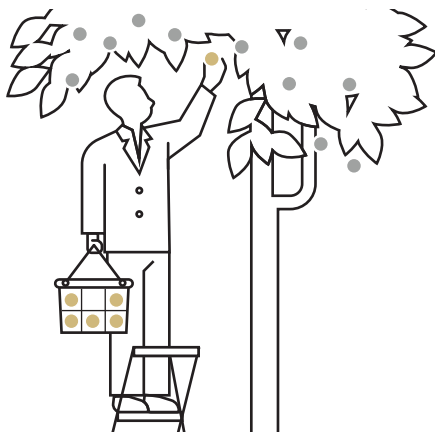


Figure 5. Use your limited space wisely. Reviewers will expect more information than what space restrictions allow, so you must prioritize the potential content (text and graphics) and select only the most critical information for inclusion in the grant proposal. Illustration by Steve Graepel.

administrative withdrawal of an application by a funding agency can feel devastating after spending months to finely craft an otherwise competitive proposal. So, invest the up-front time and energy to learn the instructions and follow them!

Few rules.

These essential points noted, it is just as important to understand that despite the many instructions grant writers are asked to follow, there are few if any actual rules when it comes to pitching your research ideas and experimental plan to peer reviewers. When developing a section of a research career development grant application, my trainees often ask: “Is it okay to propose such and such?” as if it were a legal document with strict boundaries that must not be crossed. In truth, there are few if any such restrictions when writing the research project or training plan-related sections of a grant proposal. Rather, like the courtroom attorney pleading their client’s case, you are (within obvious reason) free to present whatever arguments supporting the proposed work that will be most persuasive to reviewers (Fig. 6). Of course, those arguments must be scientifically grounded and defensible. That said, make your case using whatever ethically valid statements, concepts, observations, formatting, and other tools you have at your disposal. Be both creative and convincing in making your case. The competitive grant writer must be in equal parts an innovative scientist, skilled debater, marketing expert, and effective publicist. Those are the (non) rules in competitive grant writing. You have a lot of freedom to win the “hearts and minds” of reviewers.

New instructions.

Extending this concept, use the same creative discretion upon encountering new instructions or guidelines released by the grant funding organization that, despite your best efforts, remain difficult to understand and act on. Such situations are common in biomedical research. The grant agency will release a notice of an impending change(s) to the instructions for some grant mechanism without providing explicit guidelines or examples of how those changes should be approached regarding the specific content to be included, the

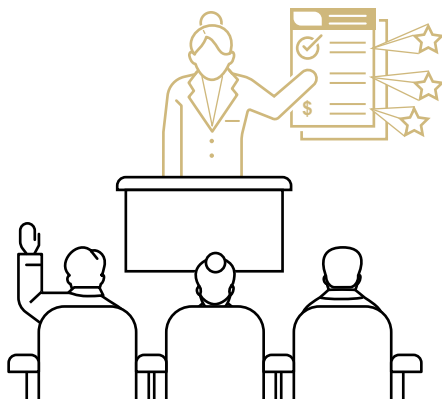


Figure 6. There are many instructions but few rules. The grant writer (*top*) is entitled to present the most persuasive, scientifically valid arguments supporting their proposed research. Be clear, control the narrative, and make the case for why your grant application should receive a strong (fundable) merit score! Illustration by Steve Graepel.

format to be used, etc. In many cases, this is intentional: the agency administrators prefer the grant writers themselves determine how best to institute those changes, assuming that the PIs (the scientists) will, organically, develop the most effective approaches. In these situations, I recommend that you establish your own interpretation of the new guideline that you can effectively work within. Then clearly frame that interpretation for reviewers in the grant application. Even if a reviewer has a different opinion of how to respond to the instruction in question, the fact that you clearly described your perspective and approach to addressing the new guideline usually will be acknowledged and respected, thus avoiding harsh criticism. Again, in these instances, proactively defining your interpretation of the intent of the information being requested usually is a sound approach for success. You have been given the license to develop a creative solution, so use it.

An alternative, but just as common, occurrence is one in which you are attempting to respond to a new guideline for which the interpretation is clear. In this situation, you should not automatically assume that reviewers are familiar with the recently released instruction. Rather, consider including a reminder to reviewers in your application that the guideline is now in place and requires the applicant to provide specific information and, importantly, that you have been properly responsive to the new directive. Doing so reduces the likelihood of an uninformed reviewer misinterpreting your compliance with the requested change and you being penalized for it with an unfair criticism. Turn such opportunities for uncertainty into a strength of your proposal by emphasizing that you have properly noted and successfully addressed the new guideline (and should be recognized for the effort).

Always “control the narrative.”

The larger point to be made in this discussion of grant writing “rules” is to always seek to control the narrative. Create the most cogent story possible and present it clearly, step by step, keeping the reviewers fully engaged as you progressively unveil the key components of the plan and supporting rationale (Fig. 6). Yes, there is an element of “Jedi mind tricks” to this approach in that you are intentionally attempting to influence (direct) the thinking of the reviewer, but I would argue that you are doing so for the greater good of all involved. On the one hand, you are seeking to convince the reviewer of the novelty and significance of your ideas; everyone understands that is the primary goal of the proposal. However, as a busy reviewer with potentially numerous other grant applications to review, I appreciate the PI explaining their thinking in an easy-to-follow process rather than shifting the burdensome responsibility of identifying, extracting, and synthesizing the critical information upon which to base the evaluation solely to me. And as a reviewer, I am willing to reward the grant writer who proposes innovative, biomedically impactful research in a cognitively conducive fashion that minimizes my time and efforts.

Speaking in broader terms, as you progress through your career, your grant writing approach should constantly evolve as you continue to gain experience in how to develop the most effective research proposals. Meaningful gains in this critical professional skill will require regular assessment of your current process and exploring new strategies to inform

the busy peer reviewer of the strengths and overall impact of your proposed research or scientific training most cogently. Do not become locked into one approach for too long a period. Be open-minded: learn, adjust, and improve the product. Achieving perfection may not be possible, but persistently seeking it is essential.

Focus on Biomedical Significance and Other “Score-Influencing” Review Criteria

Score-influencing review criteria.

As a grant writer it is important to understand that before evaluating your biomedical grant application, reviewers receive detailed information and training regarding the review criteria for your type of proposal (e.g., pilot study, standard research project, or career development application). The criteria that will be used to determine the overall merit score of your application and, therefore, have the greatest impact on funding decisions by the grant agency are designated as “score-influencing criteria”.

The score-influencing review criteria for research project type grant applications that seek funding to support the original research of a laboratory typically include the:

- scientific premise;
- biological and/or biomedical significance;
- qualifications of the PI and overall investigative team to conduct the research;
- innovation of the proposed research;
- appropriateness of the experimental approach, including the rigor and reproducibility of the methods, for achieving the specific aims and/or testing the proposed hypotheses.

In comparison, the score-influencing review criteria for research career development type grant applications, i.e., those seeking support for research training or the transition to independent investigator status, typically include the strengths of the:

- applicant;
- primary mentor and overall mentoring team;
- research training plan;
- research project;
- institutional support: including access to the facilities, major equipment, personnel, and funding (e.g., for supplies) needed to successfully conduct the proposed research training; also, support for the professional advancement of the applicant (e.g., promotion to faculty status).

Reviewers also are asked to comment on other aspects of the application, but not to factor those comments into the merit score. Common “non-score-influencing review criteria” include protection of human subjects; use of vertebrate animals; inclusion of women and minorities; biohazards; resource sharing plans; and budget.

Reviewer discretion.

All score-influencing review criteria are, by definition, important. However, reviewers are allowed substantial latitude in how much (or little) weight they place on each factor. That is, a particular reviewer might place 80% of their overall merit score on one or two of the individual review criteria. Because

of the degree of discretion allowed, the grant writer must address all the review criteria for an application as effectively as possible, not knowing which may represent the deciding influence(s) for each of the three to four independently minded reviewers assigned to critique the proposal.

Biomedical significance.

That key point noted, some grant agencies do provide recommendations regarding what criteria to stress over others. For example, many biomedical funding organizations ask reviewers to consider most strongly the significance (likely biological or biomedical impact) of the proposed research when reviewing grant proposals seeking funding for laboratory research projects. This is at least in part an attempt to emphasize “high risk, high reward” research over “safe science,” that is, research that has the potential to be more impactful, but with a higher risk of failure (conceptually and/or technically) compared with research with a greater likelihood of successful completion, but of likely lesser biomedical importance. In my experience, reviewers take such recommendations seriously and many if not most do follow that guideline. However, it is well established that overall merit ratings for grant proposals also are strongly associated with other criteria, most notably reviewers’ scores for experimental approach.

One takeaway from this discussion is that individual reviewers approach overall merit scoring of a grant application somewhat differently, reinforcing the need for the proposal writer to effectively address all the score-influencing review criteria. That important point noted, the discussion also highlights the strong emphasis usually placed on significance per se (Fig. 7). The biomedical significance of proposed research can be somewhat challenging to define. The term generally refers to the biological, behavioral, social, or other types of impact of the proposed research on the scientific community, specific patient groups, and/or the general population (society). The NIH defines “significance” using a series of questions posed to reviewers:

- Does the project address an important problem or a critical barrier to progress in the field?

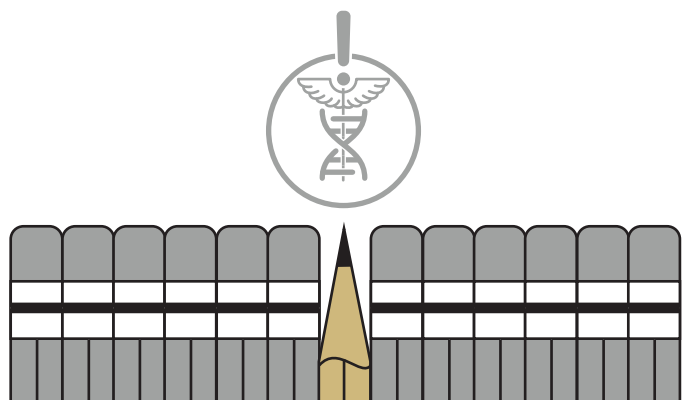


Figure 7. Focus on all score-influencing review criteria, but particularly biomedical significance. All score-influencing review criteria are important to address when developing a competitive proposal, but the biomedical significance of the proposed research (*center*) should be the most critical factor emphasized in a research project type grant application. Illustration by Steve Graepel.

- 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?

When considering potential research topics and questions for a future grant deadline, I recommend placing the greatest emphasis on biomedical significance (Fig. 7). Doing so also requires that the proposed research is “novel” because without novelty the science likely will be limited in the new knowledge to be gained and, therefore, the potential biomedical significance. Ultimately, the process of writing competitive biomedical grant applications begins with identifying a question and project that, in your opinion, have compelling significance, then convincing reviewers of that significance.

The latter goal (convincing reviewers of the significance) often is more challenging than the former. You can tell reviewers that your research idea is significant, but they may not agree with your position. After all, you are biased on that point and have an inherent conflict of interest, so reviewers might view your statements skeptically. Accordingly, always consider strengthening your argument by citing consensus viewpoints supporting your claims. For example, review the published literature and look for statements citing your topic or question as a major current research gap and a high priority target for future investigation. Review articles, perspectives, editorials, and “white papers” written by experts who have been commissioned by medical organizations or prestigious scientific journals to summarize present knowledge and identify future research directions are among the most helpful sources of external evidence supporting the significance of your ideas. Consensus medical guidelines, policy statements, publicly shared descriptions of current research priorities of grant organizations, research funding opportunity announcements from agencies such as the NIH, and medical statistics establishing the demand for more information on your research question (e.g., a highly prevalent clinical disorder with serious morbidity/mortality and few, if any, treatments) represent other potentially useful sources of expert corroboration. Citing these types of support for the biomedical significance of your proposed investigation moves the debate beyond the subjectiveness of your opinion by establishing independent sources of credibility, thus helping to substantiate your arguments. Having served on many grant review panels, I can attest to the fact that it is much more difficult to publicly challenge published consensus expert opinions than the singular perspective of a PI seeking grant funding.

Three Steps for Success: Outlining, Internal Consistency, and Editing

Outline first.

Developing a competitive biomedical grant application that will undergo rigorous peer review is one of the most challenging responsibilities of our profession, especially for early stage investigators with limited experience. My first suggestion is to invest the up-front time and effort to create a detailed outline of all the major sections of the proposal before you begin writing any narrative text (Fig. 8). One

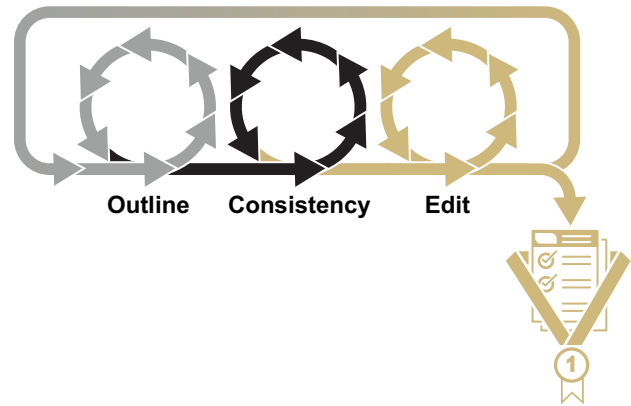


Figure 8. Three steps for success when developing competitive grant applications. Creating a detailed outline from which to write your text, ensuring the information presented throughout the proposal is internally consistent, and careful editing of your content are among the key processes for writing highly competitive (award winning) biomedical grant applications. Illustration by Steve Graepel.

approach is to identify and chronologically sequence the major sections, then do the same for the subtopics (subheadings) within each section. With the sections and subsection headings defined and in initial order, next make a list of the essential talking points and other information that should be presented within each section, then sequence those points within the section in the most logical order. As necessary, set your developing outline aside and come back to it the next day with a fresh perspective and revise the descriptions, section locations, and sequencing of the content to enhance delivery. Rinse and repeat, continuing to refine the outline until there is no further obvious way to improve the presentation of essential information. Now you are ready to write!

Working from a strong, inclusive outline ensures that most, if not all, of the key points are accounted for. Importantly, the process of translating the individual statements in the outline to a conventional narrative text largely requires only the addition of transition wording to connect the sentences and (*Voila!*) you have created an initial draft of the proposal. Your grant writing process is off and running! Although some early stage investigators resist the idea of such an extensive investment of effort for planning, strict adherence to this grant writing strategy will save substantial time in the end and yield a much higher quality end product compared with jumping into writing text without such structure and order as a beginning foundation. Doing so will undoubtedly result in many “starts and stops” while you pause to determine what the next point should be in the narrative. If you have not been an “outliner” in the past, try it and see the process through at least once before deciding. If you are already an outliner, stick with it.

Be “internally consistent.”

When it comes to writing a competitive grant proposal, consistency may not be everything, but it is critical (Fig. 8). There are few experiences more agitating to peer reviewers and therefore more likely to incur their wrath (and pointed criticism) than inconsistencies within the body of a grant proposal. To be clear, the creation of inconsistencies is a natural, even healthy marker of an effective grant writing process. If

you and your team are being thoughtful in the writing, reviewing, and revising of the text as you proceed within a section and from section to section, you will identify passages that are problematic and require modification for improvement. For example, perhaps you and your biostatistician realize the need to adjust a sample size derived from an initial power calculation during the writing of the statistics section of a proposal after already describing the number of subjects to be studied in a previous methods section, a common situation. Whatever the case, making corrections to one section of the application often requires you to make corresponding changes to one or more other sections. To avoid producing inconsistencies within and across sections of a proposal, upon identifying the need to change some component of the text, stop and either modify the information in all relevant sections at that time or make a list of changes that will need to be made later. Do not assume that you will remember every change required and “get to it later”. That is an easy trap to fall into.

Another inconsistency-generating procedure in the life of a grant writer is the need to copy and paste commonly used information from a previous application into the current proposal as a time-saving practice. In these situations, it is easy to miss small differences in a statement or fact between the previous versus current application. The problem with catching such small discrepancies is that not everyone involved in the ongoing writing process remembers the exact number in question or other facts involved when attempting to edit the developing proposal. As a result, it is important to designate some individual(s) in the writing group with knowledge of the details to work through the application to standardize and confirm the consistency of those specifics among the various sections.

Other “substrate” for inconsistency among different components of a proposal includes:

- Inadvertently varying the order of items when presenting certain types of information in multiple sections;
- Randomly using different descriptors (or abbreviations) for the same term or concept, which can confuse reviewers;
- Defining a biological process or explaining a series of processes differently across sections of the proposal.

Regardless of the exact circumstances, understand that most reviewers are careful scientists who have developed a keen eye and a sharp memory for identifying inconsistencies within a grant application. Expect them to catch all that you produce and to bring those errors to your attention in the grant critique. This single factor (internal inconsistency) can undermine reviewer enthusiasm because they may wonder if a PI who allows inconsistencies in a grant proposal also will allow them during the conduct of the proposed research.

Edit, edit, edit.

The primary tool you possess for ensuring the consistency of information presented within your grant application is the editing process. Write a section of text; edit that text; revise; edit again—repeating as necessary until no additional errors or inconsistencies can be found by any of your readers (Fig. 8). Each laboratory probably approaches the editing of research proposals a bit differently and each process, if

applied with sufficient precision and conviction, can prove successful.

For our laboratory, the process begins with persistent, focused self-editing: the primary text writer serves as the “first line of defense” against errors. That writer repeats the writing and editing cycle until they can no longer improve the narrative or identify any problems. Then and only then is the Word document shared with coinvestigators who edit the text for conceptual issues, ineffective sentence composition, typos, and other mistakes. Those edits are returned to the primary writer who must then integrate all changes into a working “master document” of that specific section of the overall application. The revised document is then sent back to the coinvestigators to confirm that their edits have been properly incorporated into the master version.

Upon completion of that step, preidentified “naïve” readers from the laboratory who are not directly involved in the development of the proposal are asked to critique the revised drafts of each section (2 readers should be sufficient for most applications). This process provides a set of “fresh eyes” from which to view the text. Parenthetically, this also serves as a useful exercise for students and junior postdoctoral fellows who presently have limited experience in grant writing; by editing the various sections of multiple grant proposals during their training, these early stage mentees gain insight into how a competitive grant application is constructed piece by piece in a rigorous manner. Word documents are designated as “final” when the PI, the coinvestigators, and the laboratory readers judge the text as clearly written and error-free. Finally, you might consider having one or two individuals scroll through the integrated pdf version of the completed proposal as sometimes remaining errors are identified during that exercise, perhaps because the appearance of the text in PDF format provides a somewhat different visual perspective than the component Word document.

Whatever your process, careful, painstaking editing is an essential aspect of developing consistently competitive grant applications. Our standard rule for determining that a research proposal is ready for submission to the grant agency is the point in the development process at which no further improvement is possible had we another week (or month) to work on the application! Effective editing is a vital mechanism for achieving that lofty product status.

Engage with Program Officers but Write Biomedical Grant Applications for Peer Reviewers

Engaging with program officers.

Most grant funding agencies encourage PIs to contact an appropriate program official to discuss the idea for a new application before development and submission. Similarly, guidelines for best practices in grant writing also typically emphasize the importance of PIs developing good working relationships with “program officers,” the latter term referring to the administrative officials in the NIH and other organizations who serve in the critical role of liaison between the program, center, or institute within the agency that is sponsoring the application and the extramural investigators who are seeking research funding.

One argument for such recommendations is that the program officer can inform the PI if their idea for a grant

application is a good fit with the agency's funding priorities. Another oft-stated reason is that the familiarity created by establishing a cordial professional relationship places the program officer in a better position to assist the PI during the proposal planning and development process, as well as after peer review. Regarding the latter period, sometimes program officers are present either in person or via videoconference during the review of the PIs application and can provide insight based on the review group discussion that is not included in the written critiques that the PI receives. Even if not present during the review session, the program officer often is able to help the PI interpret the written critiques and make suggestions on what reviewer comments to focus on and, perhaps, make recommendations regarding whether to revise and resubmit the proposal (or not). Moreover, if the PI has obtained a potentially fundable, but "borderline", merit score on the application, the program officer may be able to advocate for funding the proposal.

On these grounds, it is worth investing the time for grant applicants to establish an effective working relationship with their program officers. Such efforts would seem particularly relevant for early stage investigators, a group that, by definition, has limited experience in navigating the complex and nuanced environment of extramural funding organizations. It should also be noted that in the case of large multiinvestigator grant proposals, working interactively with a program official to obtain their permission to submit the application and, for some funding mechanisms, even developing the aims and study design of the proposal, is required.

Write grants for peer reviewers.

These key points acknowledged, it is important to emphasize the obvious fact that, with few exceptions, program officers who work for funding agencies do not review grant applications for scientific merit—your peer investigators do. This is the first phase of the two-phase review process used by most grant funding agencies (<https://grants.nih.gov/grants/peer-review.htm>), i.e., peer review of scientific merit. Identifying specific proposals for funding is the second phase of the review procedure and is the sole responsibility of the administrators (program officers/officials) of the grant funding organization. Decisions on which grant applications to fund are based on multiple considerations, including the scientific merit score produced in *phase 1* (usually the most important factor), the priority of the research topic for the grant agency, and the availability of funding. So, yes, consult with a program officer *1*) to ensure that your research concept, budgetary needs, etc., are appropriate for the agency, program, and/or funding mechanism in question; *2*) during the development of the proposal, as needed; and *3*) for assistance with interpreting the critiques. However, write your grant application primarily to meet the likely expectations of the peer reviewers (Fig. 9). In most cases, it will be the success of your aforementioned "partnership" with reviewers that represents the most direct conduit for obtaining a scientific merit score that is competitive for funding. With the leverage created by such a score, your program officer is in a strong position to help. Without an excellent merit score, there is not much a grant agency official can do.



Figure 9. Talk to your grant agency program officer (top) but write the application for peer reviewers. The grant agency program officer (top) is a helpful source of information for the applicant (left), but you should write research proposals primarily to meet the expectations of the (usually 3) peer reviewers. Illustration by Steve Graepel.

USE PEER REVIEW TO IMPROVE THE COMPETITIVENESS OF YOUR PROPOSAL

Grant Applications Need Peer Review

Goal: satisfying reviewers.

Diverse individual attitudes and laboratory cultures develop around the concept of peer review, whether grants, manuscripts, or other research documents like meeting abstracts. On one end of the continuum might be the stance that peer review is just a process that must be dealt with, perhaps even an annoyance. For those who adopt such a position, the approach upon receiving comments from a peer review process might be to make the minimal changes possible to satisfy the reviewers; to "get around" the reviewer comments the best you can while expending the least amount of time and effort; to do "whatever it takes" to move your grant score into the funding range (or have your manuscript accepted for publication). There is, of course, a practical feature to this attitude: ultimately, we all must satisfy reviewers, editors, and perhaps even grant agency officials in some cases if we are to have our grants funded and manuscripts accepted for publication. That is a requirement of any peer review system. And investigators certainly have the liberty to take that view of peer review and probably be successful. I am sure that there are plenty of examples in biomedical research if we conducted a survey.

Goal: leveraging peer review to improve the proposed research.

An alternative perspective of peer review is based on the idea that there are multiple valid perspectives on any issue in science, including those related to the research questions, aims, and hypotheses you are proposing to investigate in your grant application. You may believe, with some justification, that you and your coinvestigators are the experts on the topic—at least among the experts. However, no one, including the most capable PIs heading biomedical research grant applications, has the vision to see every possible problem or limitation associated with a research idea or experimental plan. This basic concept is the foundation of the peer review

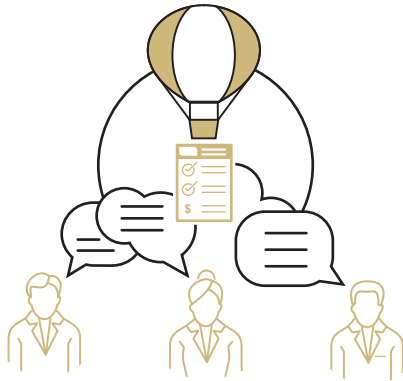


Figure 10. Grant applications need peer review. Working in isolation, no grant writer has the vision to create the perfect research plan. Rather, the comments and recommendations of peer reviewers are needed to “elevate” the quality of the grant application to produce the strongest scientific proposal. Illustration by Steve Graepel.

system: it is not simply that your grant proposal must undergo peer review, but rather that it needs to be subjected to peer review. Your application requires peer review to produce the most impactful science while using the limited resources being requested as efficiently as possible (Fig. 10). For those who operate within this conceptual framework, peer review is considered an essential vehicle to optimize the rigor and impact of the proposed research rather than a tiresome necessity of the profession.

If this alternative approach sounds appealing, achieving the end goal is attainable only via the previously discussed partnership with reviewers. Yes, some peer reviewers will turn out to be more effective partners than others. Certain reviewers will be more helpful (constructive) in improving your ideas and developing the best possible research plan for addressing your scientific aims. And yes, some reviewers may be overly negative, even unfair, in the content and/or tone of their comments. However, most peer reviewers are earnest and well intentioned. If you are open to considering their comments objectively and invest in the process of trying to understand their position, there is often an opportunity to improve some aspect of your grant proposal. Again, the process requires you to be willing to enter a voluntary, good-faith, public negotiation with peer reviewers. That negotiation has the pragmatic goal of using their comments to enhance the competitiveness of the proposal to the extent that the application receives a fundable scientific merit score. In fact, even if you receive such a score on a grant application, always work through the reviewer critiques with your coinvestigators, trainees, and staff to capture any useful suggestions on how to further improve the already compelling research you are proposing. The overarching recommendation here is never pass up an opportunity to leverage the peer review process to improve your science (Fig. 10).

Overview: Receiving, Interpreting, Considering, and Responding to Peer Review

Whatever your position on peer review, the inescapable fact is that all PIs who seek research funding from grant agencies must obtain, interpret, consider, and respond to the comments of peer reviewers. Like most aspects of grant writing,

responding to peer review is complicated—an art within the science. With most grant organizations, the first interaction after your application is reviewed will be the receipt of your scientific merit score. Based on recent funding lines, you likely will have some sense as to whether your score is fundable, might be fundable, or is not fundable. As a result, you also will have a qualitative impression about the overall enthusiasm (or lack thereof) of the reviewers. What you will not know from the score per se is the exact nature of the reviewer concerns with the proposed research and specific recommendations for improvement. The latter information will be contained in the reviewer critiques, which typically are received after a period of weeks, again, depending on the grant agency in question. Once you receive the critiques, you will need to read and interpret the comments of reviewers and, based on the combination of your score and the reviewer comments, decide how to proceed. Below I share selective thoughts on the overall process of receiving and acting on grant critiques.

Information Received in Grant Reviews

In most grant peer review settings, the applicant receives the written critiques of the three to four reviewers assigned to the proposal, perhaps after editing by the review group administrator for errors and any inappropriate wording, such as statements referring to funding status of the proposal (not the reviewers’ responsibility as just discussed). Depending on the evaluation format used by the grant organization, the reviewer critiques may begin with an overview section summarizing the reviewers’ comments on the key strengths and weaknesses of the proposed research as they relate to the major score-influencing review criteria. This “executive summary” of the most important score-influencing points from all the assigned reviewers will then be followed by the detailed set of comments describing both strengths and limitations—major and minor—from each reviewer. Some grant agency review procedures also may provide a summary of comments made during the general discussion period that follows the presentations of the critiques by the assigned reviewers. This summary of noteworthy points made during the general review group discussion often is important because all members of the group score an application, not just the assigned reviewers. It is not unusual for the overall merit score to seem more (or less) favorable than would be expected based strictly on the comments of the assigned reviewers, leaving the grant PI a bit perplexed. Sometimes this is due to the influence of the general review group discussion on the final scoring so that discussion can be important.

After receiving the written critiques, the next step is to read and interpret the information, the latter representing the initial part of the “art” for effectively responding to grant reviews. Responding to your interpretation of the reviewers’ comments is the second part for those proposals that the PI and investigative team decide to revise and resubmit.

Reading and Interpreting Reviewer Comments

Reading and accurately interpreting the comments of the reviewers are the critical first steps upon receiving critiques of your grant application. If the reviews are not carefully

read, are carefully read but misinterpreted, or some combination of both, your ability to accurately consider the reviewers' comments and make an informed decision about whether to revise and resubmit the grant proposal will be hindered. Given the importance of this step, the following suggestions may be helpful when attempting to read and interpret the comments of reviewers (Fig. 11).

Adopt a proper “mindset” before reading the reviews.

As highlighted in the preceding section, the comments of peer reviewers should be viewed as a unique source of expert insight—an invaluable resource for improving your proposed research rather than an obstacle to overcome. Fully “harvest” the perspectives they share and thoughtfully contemplate their recommendations, rather than just attempting to navigate through them.

It is “strictly business.”

There is a scene in the iconic dramatic film *The Godfather* in which upon being accused of taking the prior actions of a villain too personally when recommending an appropriate retaliatory response, the character explains to his accuser why that is not the case, ending with the classic retort that his proposed plan of action is not personal, but rather is “strictly business”. This line of reasoning also is important when reading and interpreting reviewer criticisms in a grant critique. Even though the comments may, in tone and/or content, feel personal, do your best to deflect any such sentiment. Instead, work within the strict construct of “problem-solving.” Ask yourself and your colleagues: What issue is the reviewer raising in their comment? Seek to understand the statement in a purely scientific or biomedical context to best position yourself to address the concern most effectively in a proposal resubmission. Suppress any negative emotion as much as possible and focus on improving the proposed research as viewed through the lens of the reviewer.

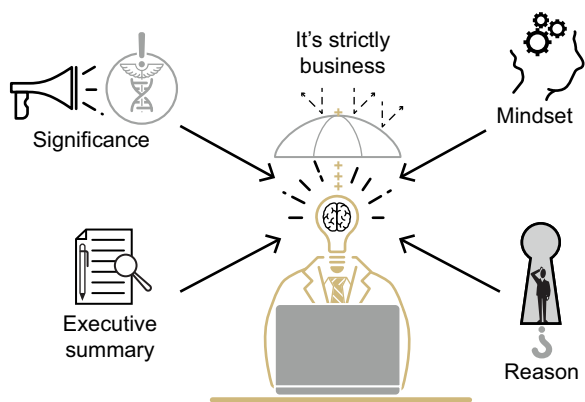


Figure 11. Reading and interpreting the comments of grant reviewers. When reading and interpreting reviewer comments in grant critiques (clockwise from lower left), the grant applicant should 1) focus on the major strengths and weaknesses emphasized in the executive summary section; 2) emphasize comments related to the biomedical significance of the research because those are usually the most important; 3) try to “deflect” any negative emotions and concentrate on problem solving; 4) have the mindset that the critiques represent an invaluable source of insight for improving the application; and 5) recognize that there is a reason for every reviewer comment and you should try to identify the reason to improve the proposal. Illustration by Steve Graepel.

Focus most on comments presented in the “executive summary” section.

If your grant reviews include some type of “executive summary” section that emphasizes the most important factors influencing the scores of the assigned reviewers as well as the key points made during general discussion (all members of the review group), focus your greatest attention on those comments. Again, that section should be written by the review group administrator and represent the most important score-driving strengths and weaknesses identified by all the reviewers. The major strengths and weaknesses expressed by each individual reviewer also are important and should reinforce the points emphasized in the overall executive summary section.

The “significance” and “experimental approach” review criteria-related comments carry the most weight.

As discussed in the ‘GENERAL RECOMMENDATIONS FOR EFFECTIVE PROPOSAL WRITING’ section of this Viewpoint, reviewer comments regarding the significance of the research and the proposed experimental approach typically are most strongly associated with the overall scientific merit score of proposals, at least in the NIH system in the U.S. As such, although comments made under any of the score-influencing review criteria headings may be important, concerns and recommendations regarding the significance and experimental approach usually warrant your greatest attention. However, there also is a helpful rule of thumb to consider when interpreting comments related to these two influential review criteria: if reviewers are enthusiastic about the biomedical significance of the proposed research, you likely have a solid foundation to build on in a potential revision/resubmission process. In that situation, it may be possible to address concerns expressed about the experimental approach and other review criteria to increase the competitiveness of the application for funding. However, if reviewers feel that the biomedical significance of the proposal is weak or only moderate, then the proposal may not be redeemable as presently constructed and would need to undergo major conceptual and/or structural revision to make it competitive for funding in a future resubmission. Stated another way, many if not most concerns with other review criteria can be addressed, but lack of enthusiasm for the significance of the proposed work is almost always fatal for a grant application.

There is a reason.

Contemporary peer review critique formats, including those used by the NIH in the U.S., often are designed for brief, focused (e.g., bullet structured) comments rather than longer, more fully developed explanations of concerns and recommendations. In such critique formats, the difference between statements that are “sufficiently clear and succinct” (to allow for precise interpretation) versus “cryptic with uncertain meaning” is a slippery slope, and you will encounter the latter situation with at least some of the reviewer comments in most grant critiques you receive. This can be (and often is) a frustrating experience for grant writers. It is important to appreciate, however, that no matter how seemingly obscure or uninterpretable the statement on first (or even repeated) reading, there usually is an underlying point worth noting. Accordingly, you need to invest the time and energy to

determine what the reviewer is referring to and why they are making that comment. Try to find the origin of the point. Sometimes you will identify the meaning somewhere at the intersection of that “vague” comment and a passage of text in the grant application. In other cases, the comment may, unfortunately, remain a mystery. Either way, give the process your best effort because the comment may represent the difference between successfully addressing a reviewer’s concern in the grant resubmission versus being completely ineffectual. If the comment focuses on what seems to be a critical point, but after due diligence remains uninterpretable, you do have the option to contact the grant program official for insight. This likely will require the official to contact the administrator of the review group, who, in turn, must contact the anonymous grant reviewer in question, hope to receive a clearer explanation from that reviewer in a useful time interval for resubmission, and then relay the information to you. This is obviously a logistically cumbersome process not to be used too frequently or for concerns that appear to be lower in impact, but rather to be held in reserve for major, potential score-influencing situations.

To Resubmit or Not to Resubmit: That Is the Question!

If your grant proposal does not receive a sufficiently strong scientific merit score to be selected for funding by the grant agency, you have at least three options:

1. Revise and resubmit the original application without extensive structural changes such as major modifications to the original specific aims;
2. Develop and submit a new application based on those components (specific aims and associated experimental approaches) of the original proposal that were well received by reviewers and replace poorly reviewed components with new content;
3. Abandon the entire application and move on to another proposal idea.

Deciding among these (or other) alternatives depends on the unique situation presented by the grant application and critiques in question. In some cases, the decision is straightforward because you received a strongly favorable scientific merit score with correspondingly enthusiastic reviewer comments (*easy option 1* choice) or, in contrast, a strongly unfavorable merit score and uniformly negative reviewer comments (*option 3*). However, the reviews of many, if not most, applications fall somewhere in the middle without an obvious indication of which direction to take. In these settings, the comments of the reviewers are a mix of enthusiasm and lack of enthusiasm. That mix may be due to differences of opinion among the (usually) three reviewers. For example, one reviewer may be highly enthusiastic, one moderately so, and the third not at all. Alternatively, all three reviewers may have scored the application with moderate enthusiasm citing a mix of strengths and weaknesses across the score-influencing review criteria. For example, one reviewer may have scored the significance of the research and the PI and investigative team highly, but had serious concerns with the proposed experimental approach, whereas the other two reviewers questioned the significance and innovation of the research but had only minor concerns with the experimental

approach. These proposals that receive mixed reviews pose the greatest dilemma to grant writers: revise/resubmit the original application or develop/submit a new proposal using the most well received parts of the original application?

Established PIs have developed their own decision-making process for such situations based on some combination of instinct and experience, including trial and error. Early career stage PIs will have instincts, of course, and some, but limited, experience depending on their involvement in the grant writing process during scientific training. In either case, there are many different considerations for deciding on an approach in these situations. However, for many PIs, the decision to revise and resubmit is based largely on two requirements:

- There must be a clear foundation of enthusiasm for the proposed research expressed by most, if not all, the reviewers, including strong, uniform support for the biomedical significance of the work (Fig. 12);
- Significant weaknesses, including all major limitations described in the executive summary and individual reviewer critiques, can be resolved to the reviewers’ satisfaction.

In most cases, the decision comes down to a visceral, qualitative sense for the collective level of reviewer enthusiasm for the original proposal rather than a quantitative list of pros and cons. Again, experienced PIs may have an advantage in this setting, but junior investigators with good instincts, thinking objectively, and focusing on the key considerations aforementioned should be able to make an informed decision in most instances. Moreover, the decision should not be made by the PI in isolation, but rather in conjunction with the comments and recommendations of the coinvestigators and other members of the laboratory grant writing team. Following this type of process usually leads to a consensus opinion on the question of “to resubmit or not to resubmit.”

Advice for Revising and Resubmitting Grant Applications

For those instances in which you decide to revise and resubmit the original grant application, the next question is how to do so most effectively. Again, proper mindset is an important starting point: you must view the process as an opportunity to leverage the comments of the reviewers to

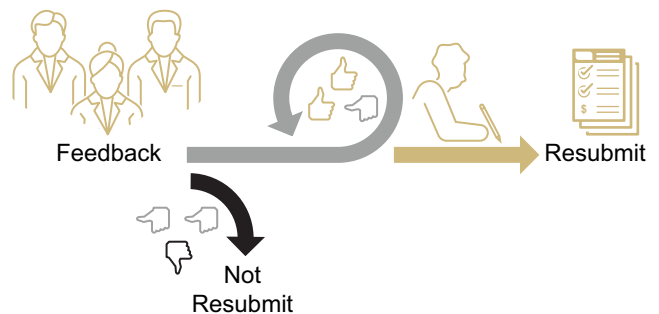


Figure 12. To resubmit or not to resubmit: that is the question! The single most important determinant when considering resubmitting a grant application is whether the original proposal had a clear foundation of enthusiasm from most, if not all, of the reviewers. Illustration by Steve Graepel.

enhance the impact and rigor of the proposed science; if you accomplish that objective the merit score likely will improve, as well. During the revision process, your responses to the concerns and recommendations of the reviewers of the original grant application will consist of some combination of 1) rebuttals to their comments presented on a separate page or section of the revised application and 2) corresponding changes to the text of the original proposal (for those rebuttals that require revisions). Note that this process should be followed with the knowledge that your rebuttals and text changes may be viewed by the original reviewers, a completely new set of reviewers, or some combination of the original and new reviewers (most likely). The eventual selection of reviewers for the resubmitted application is out of your control and, therefore, not worth the energy or time for speculation. With these comments as general background, the following thoughts and recommendations may prove useful as you develop the responses to the original reviewers' comments and any associated revisions to your grant proposal (Fig. 13).

Organize the comments of the reviewers.

The first step in the revision process is to extract the key concerns and suggestions from the original grant critiques that you identified during the “reading and interpretation” phase and organize them in outline format using some order that is cognitively effective for you as the grant writer, as well as the reviewers. The format used could be based on the comments from each reviewer (using the reviewer or critique number as the subheading for the comments-responses that follow) or by the subject of the comment (without reference to the reviewer). Either approach can be effective. If some of the concerns were expressed by more than one reviewer, it may be more space-efficient to organize by subject rather than by reviewer. If you wish to prioritize the collective comments of the reviewers and your associated responses by overall importance, usually you will use a subject-based approach. Practically speaking, a subject-based format often is necessary because there are simply too many individual comments that

require responses to fit into the allowable space (typically one page) and you are forced to consolidate the comments from different reviewers related to a particular subject (concern) to meet page restrictions.

Develop earnest responses to each comment.

Once you have the comments of the reviewers properly organized, work through each point with your grant writing team and try to reach a consensus on the most effective response to each reviewer's concern and recommendation. The initial effort in this step should occur during the “reading and interpretation of critiques” phase of the revision process to reduce the number of meetings, especially for coinvestigators who are busy directing their own research programs. It is important that you address as many of the reviewer comments as possible, including all major criticisms, not just those concerns that are most straightforward (the “low-hanging fruit”). The key buzz term with these sections of grant resubmissions is “responsiveness”—how responsive the PI has been to the comments of the reviewers in the original critiques. Your responsiveness will be judged by both the number of comments you respond to and the effectiveness of your responses in addressing the concerns and recommendations of the reviewers. It will not always be possible to completely satisfy a reviewer with your response, but what you can control is the number of comments that you at least attempt to address in a good-faith manner.

Be profusely “professional.”

Regardless of whether the comment to which you are responding is one that you view as reasonable (constructive) or inappropriate (misinformed, unnecessary, annoying), it is imperative that you structure and express your response in a professional manner. This means using language that conveys a suitably civil and respectful tone to the reviewers. Do not choose wording that is directly critical of the reviewer, even if you believe the comment was baseless, wrongheaded, or even completely ridiculous. There are many ways to make your point without sounding overly negative or critical of the reviewer in a manner that might evoke a defensive or otherwise antagonistic counterresponse from them. Find a way to present your argument in a clear, firm, but appropriately diplomatic fashion. Remember: it is strictly business.

Optimize use of your limited space.

Because of page restrictions, you will not have sufficient space to provide a fully developed response to each reviewer's comment in the revised application. As a result, you will need to expertly construct your limited text, being as concise as possible. Doing so requires, in part:

- Prioritizing your space to address the most significant issues raised by reviewers as thoroughly and definitively as possible;
- Allocating more space to responses that involve multiple points or are otherwise complicated, and less space to reviewer concerns that are more straightforward and can be addressed more succinctly;
- Not including “extra words”, defined here as words that can be deleted without altering the meaning of a statement.

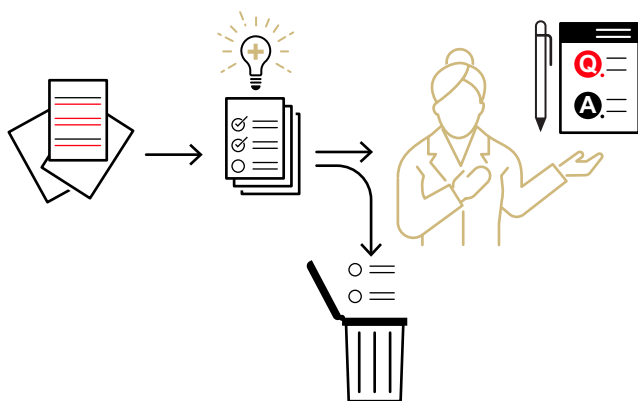


Figure 13. Advice for revising and resubmitting grant applications. Responding effectively to reviewer critiques entails (L to R) 1) properly organizing reviewer comments; 2) developing “positive” responses to each comment and appropriate text revisions in which you establish the narrative; 3) choosing your battles and optimizing your limited space—what to leave in vs. out (*bottom*); 4) being earnest, professional, and empathetic when responding to reviewer critiques, with the collective goal of creating the most competitive revised application possible. Illustration by Steve Graepel.

Effective space management in the responses-to-reviewer-comments section is often more critical than for other sections of the application. To achieve that goal, you and your colleagues will need to edit this text repeatedly to use the fewest words possible to make your arguments.

Practice reviewer empathy here, as well.

This section of the revised application requires effective application of your newfound appreciation of reviewer empathy and its practice. The overburdened reviewers who have been assigned your renewal application will expect this section to be properly organized and spaced, well written (articulate), and scientifically focused. They will seek to capture the essence of whether you have been adequately responsive (to the comments of the original reviewers) in the most time-efficient manner possible. Consider the following suggestions to facilitate their efforts:

- Use bold subheadings that clearly reflect the issue in question;
- Construct cogent responses that are easy to interpret;
- Whenever possible, explain your options and decision-making;
- Be honest and transparent. Savvy reviewers know the difference between a sincere, scientifically based response and “hand-waving” (i.e., appearing to be responsive to a concern without offering anything substantive). They do not appreciate the latter and usually will let you know it in your critique;
- Never sound defensive or evasive; reviewers appreciate a “direct” response to a “direct” comment.

When in doubt, you need to establish the narrative.

With reviewer comments that, despite your most diligent efforts, defy definitive interpretation, you must be proactive in establishing the narrative. Identify the most reasonable interpretations, select the one you feel can be addressed most effectively with a persuasive scientific argument, and respond accordingly. I often structure my response by diplomatically stating that the reviewer’s comment was not clear, but we are interpreting the comment to mean such and such. On occasion, this strategy can backfire: the reviewer may object, stating that you misinterpreted their (presumably clear) comment and, therefore, your response is off the mark. However, in my experience, upon rereading the comment in question and a bit of self-reflection, most reviewers recognize a less-than-ideally articulated comment on their part and, if your interpretation and corresponding actions are sensible, will accept your argument as properly responsive. The main point here is that when in doubt, you need to seize the initiative and control the narrative rather than sounding ambiguous to cover all possible explanations to a vague reviewer comment.

Positive presentation.

To begin on a positive rather than a negative note, before presenting your responses to reviewer concerns, start your responses-to-reviewers comments section by emphasizing all the strengths of the application described by the original reviewers. Again, be concise so as not to consume precious space needed to reply to reviewer concerns and

recommendations for improvement. I usually limit this description to a short paragraph consisting of no more than approximately three lines of text. In addition, when creating the bold subheadings describing specific reviewer concerns, consider wording that represents a more neutral position on the comment in question. For example, if a reviewer criticized your original proposal for “not providing any mechanistic insight” you might paraphrase using a less negative subheading entitled simply “Mechanisms” or “Mechanistic insight.” Within the previous recommendation of “honest and transparent,” look for opportunities to maintain a tone of optimism and positivity in this critical section of your resubmitted application that might favorably influence the perspectives of the reviewers.

Choose your battles.

The critiques of your original grant application will have several comments from each of the three to four assigned reviewers to which you need to respond and, possibly, additional remarks from the general discussion of the entire review group. It is not unusual to receive, literally, dozens of collective concerns and recommendations that must be addressed. It also is likely that you will disagree with many of the comments. However, it is important that you not argue all or even most of the comments made by reviewers. Rather, you need to be selective: “choose your battles,” as the adage goes. Perhaps compromise less on issues of real functional significance that you believe will negatively impact the proposed research while attempting to accommodate reviewers on less critical points. Regardless of approach, it is important that you look for opportunities to be responsive to each potentially merit score-shaping comment of the reviewers. In situations in which I believe the reviewer to be mistaken and the comment unhelpful, I will try to use what I refer to as a “one-two punch.” This is an old boxing term referring to a left-handed “jab” immediately followed by a “right cross,” but the term actually refers to any effective combination of two entities. In this case, I first point out, respectfully, that the comment is unfair and why. This is the first punch, delivered with the goal of encouraging the reviewer to reconsider the comment and hopefully soften their originally critical position on the issue. I then try to give them something related to their original concern or recommendation (the second “punch”), attempting to meet them “part way.” With this type of approach, on the one hand, you are defending your proposed research plan on a point of importance for maintaining scientific rigor, whereas on the other hand, formally acknowledging and being responsive to the reviewer’s comment. No strategy is foolproof, of course, this one included. However, this is another tactic that in my experience is usually successful and, therefore, worth considering when the situation warrants.

Leveraging Peer Review to Strengthen Your Proposal: Endgame

Peer review is a unique and valuable resource: a precious “gift” that provides numerous opportunities to improve your research ideas and experimental approach, while enhancing

the biological and/or biomedical impact of your science. Most grant applications do not receive a sufficiently strong merit score to be chosen for funding on the initial submission and must undergo revision/resubmission or complete redevelopment to eventually be awarded. As such, understanding the nuances of grant peer review and developing effective strategies for addressing reviewer comments is essential to obtain (and sustain) extramural research support for your laboratory. It is in your best interest to invest in this process and to become as skilled and experienced as possible for your professional success and that of your research program.

VIEWPOINT PART 1 SYNOPSIS

In this Part 1 of the Viewpoint (4), I began by discussing the importance of writing competitive biomedical grant applications, noting the many challenges involved, and establishing my extensive experience on the topic. This introduction was followed by a lengthy perspective of the essential process of peer review of research proposals, peer reviewers as de facto partners in the development of grant applications, and how to most effectively work with reviewers to achieve success. Next, I shared several general strategies, recommendations, and insider maneuvers for competitive proposal writing. Finally, I discussed how to leverage the comments from peer reviewers to strengthen the science and competitiveness of grant applications that require resubmission. In Part 2 of this Viewpoint (5), I will share additional thoughts and tactical approaches aimed at enhancing the quality of specific aspects of research proposals, and in Part 3 (6), I will discuss strategies for writing competitive research career development grant applications.

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AUTHOR CONTRIBUTIONS

D.R.S. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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