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How to Prepare for and Write a Grant: Personal Perspectives

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Success in academic medicine is driven in large part by obtaining grant funding. Resources are limited even in the best of circumstances; therefore, competition is frequently fierce. Herein we outline our personal perspectives[1] gained over decades of (painful) apprenticeship and mentoring as well as planning, writing, rewriting and reviewing grants. We focus on independent investigator-initiated (ie, R01, VA Merit Awards) applications, although many of the concepts are applicable to mentored or similar career development award applications and summarized in recent publications.[2–6]

Timing of Grant Submission

Among the pressing questions are: When is the best time to write a grant and what steps optimize the likelihood of a successful outcome? The answers depend on your career stage (eg, fellow vs faculty), the type of grant you envision (eg, career development type [K-series] vs independent investigator type [R-series]) and (a major determinant) how much preliminary including published data you already have. For clinical and epidemiologic grants, the availability of or access to relevant, well-characterized patient cohorts or biological samples is key. In the context of applying for your first (ie, A0 application) independent (R01 or equivalent) award, a key consideration is the timing of the submission in relation to publications. Ideally, a new independent grant submission will be based on a foundation of $\geq$1 or 2 recent (within 18 months) publications, substantiating the proposal and reflecting your role as first or corresponding author. Reviewers will understand if those publications have your mentor as a coauthor (ideally not corresponding) and their inclusion (as coauthor) should not jeopardize your application.

Other Resources Needed to Accomplish the Proposed Study

Verify resource and time allocation (division/department head letters of support and institutional commitment) and collaborative arrangements for key resources. Finally, assign sufficient time to review, refine, and integrate the hypotheses and aims with input from colleagues and senior mentors to provide feedback. Of note, some institutions arrange formal internal reviews, or offer to pay external reviewers to critique grants before submission and are worth considering.

Key Points

- Plan initial (A0) submission in relation to recent high-impact publication(s).
- Do not waste a review round with premature application; it is difficult to go from unscored to a fundable score on A1 application.
- Allocate $\geq$6 months to preparation of a new (A0) R01 application to optimize organization of aims as well as editing and rewriting. Find examples of previously funded grants.
- Life is short; invest your time in projects you like and want to do, and then apply for grants to accomplish these projects rather than pursuing projects that simply follow the money trail.
- Assemble a team that includes individuals who you think will actually help with the content, methods, and editing. Discuss with, and if appropriate include as coinvestigator, mentor or senior colleagues early on. Draft letters of support for all investigators on the team. Do not wait until the entire proposal is written before you engage the research team.
- Plan to review all biosketches and personal statements and make sure they are updated, well-formatted, and fit the purpose of the specific grant.

Preparation and Anticipation

Is the Grant Mechanism Appropriate for the Proposed Study?

Most grant applications are written in response to an announcement or statement of interest from the funding

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.11.025

agencies. Are your ideas responsive to the needs of the funding agency? We recommend early contact with the program officer to ensure that there is general interest in your idea. Verify the required resources will be adequately covered with the allowed budget and duration of the awards.

Engage Statistical Help Early

For clinical grants in particular, both feasibility and resources are highly correlated with anticipated recruitment and duration of follow-up, if any; therefore, we recommend at least a "back of the envelope" power and sample size calculation and project budget early on in the planning process.

Updated Grant Requirements

Even experienced investigators need to read and review updated grant requirements (publication NOT-OD-16-011 discusses in detail both application instructions and review language that have been updated for the National Institutes of Health [NIH] applications). These instructions and requirements frequently change.

Tell a Story and Anticipate Questions

The purpose of writing a grant is to tell a story in which you influence, excite, and convince the reviewers and funding agencies. Try to anticipate the questions that reviewers will ask and frame your entire application to reflect these expectations. Reviewers will ask 5 distinct general questions.

Hypothesis. Reviewers (very much) like hypothesis-driven research. Is there a clearly stated, central hypothesis? Is the central hypothesis interesting, novel, and timely? In other words, will the outcome really advance knowledge and exert a sustained impact in the field? Is the hypothesis embedded throughout the application? Descriptive or observational studies usually do not fare well.

Feasibility. Reviewers will scrutinize applications from junior faculty submitting an independent award to answer whether you can actually do what you propose. They will ask if you are using state-of-the-art approaches. They will expect you to justify that you have the technical expertise and institutional resources to undertake new and untested approaches. They will ask if the experiments you propose can be accomplished with the reagents (eg, animals or cell lines) in hand. If key reagents are not in hand or, for example, if the phenotype of knockout mice is yet to be verified, reviewers will expect you to justify contingencies. For clinical and epidemiologic research proposals, verify access to the populations and patient material you propose and provide contingencies for patient accrual. Reviewers for these types of grants will ask if the proposed studies are feasible within the timeframe proposed. They will evaluate the sample size and power calculation sections closely. Perceived low-power or small sample sizes are usually fatal flaws that reliably lead to a poor score.

Investigator and Environment. The key metrics include the applicant's past performance (background, training, earlier publications) and overall (but especially) recent productivity, namely, those publications underpinning current proposal. Reviewers will ask if successfully accomplished, will those studies build on an independent trajectory? In addition, and particularly for faculty proposing a new independent application, it is crucial to demonstrate strong mentorship as an ongoing (environmental) resource in troubleshooting.

Impact. Reviewers will ask if addressing the aims as outlined will exert a sustained impact and influence the field. Does the proposal challenge an existing paradigm? Will the findings advance knowledge of the pathogenesis, treatment or prevention of disease? Solicit input from senior colleague or mentor to align the goals and aims of the application to emphasize impact.

Significance. Your proposal must address why the questions are important, how the answers address an unmet need and their relevance to disease prevention, pathogenesis, treatment, or outcomes (also, see Scientific Premise).

New Sections (2016). It is critical to include a formal section on rigor and transparency (ref NOT-OD-16-011). In addition include a sentence (or few) addressing the scientific premise, summarizing the background, preliminary data, and how your proposal addresses weaknesses or gaps in the field as outlined in the background and preliminary data. This item is now included as part of significance criterion for peer review. Rigor and transparency relates to the strategies to ensure a robust and unbiased approach and will influence overall impact score. Similarly, consideration of relevant biological variables (age, sex) is a key component for all studies including vertebrate animals or human subjects whose inclusion will influence overall impact score.

Key Points

- The scored review criteria are significance, investigator, innovation, approach and environment.
- Demonstrating your hypotheses, and addressing the feasibility and impact, are key determinants of scores related to significance, innovation, and approach.
- Know what the reviewers expect (and score you on) and make sure that you cover all of these points in the grant application.

Approach

We highlight some key issues pertaining to specific aims, background and significance, preliminary data, and research plan sections of the proposal.

Construct a Thumbnail Outline

Opening statement should summarize the background that informs objectives and justify a central, overarching hypothesis. Use the active voice, ("Because of XXX, we will examine YYY…). Consider a summary figure in which the aims are integrated into the relevant pathways and

hypotheses. This figure can be placed within the specific aims or in the background section.

Summarize Key Preliminary/Background Data

Identify core observations that inform and guide the overarching hypothesis. Avoid extensive summary of past accomplishments. Use short declarative sentences such as, "We have shown XXX and so we will determine how YYY influences outcomes in patients with ZZZ." Summarize pilot data demonstrating the validity of the rationale for the proposed study. These data establish your ability and feasibility to conduct the proposed experiments.

Organize Aims in Sequential, Numerical Format

Outline specific objectives within a testable (sub)hypothesis for each aim. The central overarching hypothesis and rationale should provide linkage between aims. Organize the aims in a logical, hierarchical manner. Justify the general approaches proposed for each aim so the reviewer understands the themes and experimental objectives. Avoid structuring aims with a simple yes/no outcome. Restate these aims exactly in the research plan.

Keep It Simple

Imagine describing to a senior colleague who is not an expert what you propose and why it is important. Limit experimental detail; reviewers will focus on the big picture (significance and impact).

It is crucial that you summarize in explicit detail the significance of the proposal. Some applications embed significance on the specific aims page, others in the background section; we prefer the former. It is also crucial to summarize explicitly the innovation of the proposed work. Some applications embed significance on the specific aims page, others in the background and significance section.

Key Points for Background and Significance

This is an important component of the application and, used strategically, sets the tone for your experimental plan. The general objectives include the following.

- Demonstrating your understanding of the field, recognizing contributions of others (significance).
- Clearly showing that the general research area is important and worthwhile exploring further; for example, a biomarker study may not be worthwhile if the condition is rare, does not impact morbidity or mortality, or has no good treatment (significance, impact).
- Identifying unmet needs and outlining the next, most logical steps for research in the field (significance, impact).
- Illustrating novelty and importance of your proposal (innovation).
- Include really effective illustrations to outline your experimental approach; these are key for a good and simple section that sets up your later proposal and that can be easily followed by reviewers.

Detailed Objectives

- Link your preliminary findings to core hypotheses and to the aims. Establish a solid scientific premise (now contributes to overall impact score).
- Establish direct connections between your most compelling findings and your research plan (feasibility).
- Reassure the reviewer that your proposal is seamlessly integrated into the field and represents the next logical step (significance, impact).

Traps to Avoid

- Rambling background or review-like summary with lengthy historical perspectives. Do not try to educate the reviewer.
- Dangling anecdotes and oblique references to "interesting" or "intriguing" findings.

Preliminary Data

Reviewers will ask if preliminary and/or published data lead into the aims of the proposal. Preliminary data sections can also contain previous experience in conducting studies with similar methods (eg, clinical trials, survey studies) or track record of collaborations with relevant coinvestigators. We recommend that each aim contain its own relevant preliminary data (vs one section for all preliminary data).

Experimental Plan

This section is a primary factor in assigning overall impact.

Key Points

- Scientific rigor is a required component. Allocate several lines to verify statistical procedures, data analysis, subject inclusion/exclusion, and so on. Especially for studies dealing with human subjects, detail the sampling frame, inclusion and exclusion criteria, and recruitment and study procedures. Power and sample size should be a clear separate section. Show the reviewers that the proposed measurements are valid (measure what they are supposed to measure), reliable (consistently measure the same thing in the same manner), and complete (performed in all study subjects). The measurements need to be defined for the main exposure or intervention, outcome, and especially in human studies for confounders and effect modifiers. The main possible misclassification

or biases need to be described along with potential consequences and ways to mitigate them.

- Consideration of biological variables, particularly for experimental animals, including sex, age, source, housing, and genetic strain is now a required component (see NOT-OD-15-102).

Key Tips for Figures

- Use color and ideally should be stand-alone. The legends must be legible (minimum 9-point font) and summarize findings rather than the experimental approaches.
- Do not copy and paste legends from manuscripts. Grant legends should summarize results with caveats and alternatives that inform your aims.

Key Tips for Formatting

- Do not overcrowd pages. White space provides visual appeal and is much easier on reviewers. Many reviewers print applications and like to write notes in white space.
- Use identical font type throughout the proposal (suggest Arial) including both figure legends (9 point) and text (11 point).
- Experimental design: Organize each aim and subaim exactly as in the specific aims page. Embed the relevant preliminary data adjacent to the corresponding aim or subaim.
- Consider a modular approach: Rationale (with summary of preliminary data)/experimental approach/anticipated results with potential caveats/pitfalls and alternative considerations. Reviewers rarely have several uninterrupted hours to review an entire application and the modular framework provides natural breakpoints.
- Highlight new methods/concepts: Emphasize innovation and environment. For new investigators, feasibility with technical expertise and other environmental resources can be placed in the biosketch.
- Try to achieve balance across all aims. Never propose just 1 aim; 2 (acceptable) or 3 aims are preferred and can be amplified with subaims; >3 aims become difficult to balance in space and strength. One weak aim will sink an application, so strive for balance. Aims should not be dependent on one another, such that if the experiments in aim 1 do not work, you cannot proceed with aim 2.
- Organization and flow: Create a logical flow to the proposal. Link the aims thematically along with their contingencies and alternatives.
- Other tips and pointers: For each aim, allocate one-fourth for rationale, two-fourths (ie, one-half) for a detailed experimental proposal, and one-fourth for anticipated outcomes and alternative interpretation/troubleshooting. Document how the predicted outcomes will advance the field and represent durable impact. Detail contingencies for all possible outcomes with feasible approaches connected to new alternative hypotheses.
- Provide a time-line for each aim (year 01, 02, etc). This timeline at the end summarizes and brings together all the aims again. Particularly for new investigators, speculate on possible future directions.
- Secure letters of support from key investigators (eg, histopathologist, biostatistician).
- Environment: Are the facilities, resources, collaborators and mentorship aligned? Optimize space allocated within the 5 page biosketch to emphasize background training, institutional resources, collaborative support, and mentorship. The biosketch needs to updated, well formatted, and relevant. NIH biosketch contains sections on contribution to science and a personal statement; these sections especially for collaborators need to be carefully written to be aligned with the proposal and emphasize certain aspects of relevant expertise or collaborative arrangement.

Other Considerations and Additional Review Criteria

There are other (unscored) components, including protections for human subjects, vertebrate animal use and welfare, and biohazards. There is a new required section for authentication of key biological and/or chemical resources (not included in the 12-page limit). Examples include key cell lines, specialty chemicals, antibodies, and other biologics that are not standard reagents. There are also sections to justify applications from foreign organizations, a section to describe resource sharing (for unique reagents that may be generated in the course of the studies proposed), and a section for justification of multiple principal investigator applications in which the oversight and management of the project must be detailed and mechanisms for resolving conflict should be discussed. The bibliography is not included in the page limit but chose literature citations that are representative and inclusive without being overwhelming. Review for incomplete and duplicated references even if software (EndNote, Refman) is used. Ensure that all edit marks and inserted comments are incorporated or removed.

Introduction to Revised Applications

This is not easy, but begin by thanking the reviewers for their suggestions and, in a few lines, summarize the major changes in response to the previous critique. Use phrases like “in response to prior review.” Provide a point-by-point response to the major concerns of each reviewer. Be selective. This is an opportunity to emphasize positive changes and to suggest how these now strengthen the application. Summarize new preliminary data and indicate how this strengthens a new specific aim or subaim. Indicate where relevant that these new findings are included in figure X in

the revised application. Do not insert lengthy discussion of material that you have eliminated, particularly in response to the reviewers' suggestions.

Useful Tips and Resources

A systematic review[6] of published papers published from 2000 to 2012 identified many recommendations for writing successful grant proposals, extending the themes discussed above. In addition, the office of extramural research (available from: http://grants.nih.gov/grants/oer.htm) has many useful suggestions and a regularly updated service with blogs and updates on peer review (available from: http://nexus.od.nih.gov/all/nexus-by-date).

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Conflicts of interest
The authors disclose no conflicts.

Supported by the National Institutes of Health (DK-56260, HL-38180, DK-07130, DK-52574 to NOD) and (DK58338, DK24-04-107, CA190776, CPRIT RP150587 to HES) and to the Center for Scientific Review for the opportunity and privilege of participating in peer review.