Statistics Grants from the NIH

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These days, successful grant writing ranks alongside teaching and research as an indicator of success in the academic environment. Young assistant professors fresh from their doctoral or postdoctoral training are usually provided with one to three years of start up funds to get their own research agenda established. Within a year or so, however, most need to start planning a grant submission if they want to be assured of continued support for their methodological research. There are many different sources of support. While the National Science Foundation is probably the most common source of support for more theoretical research, the National Institutes of Health (NIH) is by far the biggest supporter of more applied methodological research that is motivated by applications in medicine and health. The purpose of this article is to provide a short overview of how statistics grants are generally reviewed at the NIH and to provide some guidelines on preparing a successful grant application. The article was jointly commissioned by ASA President's Committee on Research Funding in Statistics (N. Flournoy, Chair, W. Rosenberger, J. Gentle, N. Singpurwalla) and the Committee of Presidents of Statistical Societies (COPSS). The article represents a synopsis of a presentation given at a Young Investigator Workshop held as part of the ENAR Spring Meetings in March 2001. Although a number of people have made helpful comments on the article, the views expressed here are largely personal ones, reflecting my own experience with grant writing as well as my recent service on the Study Section that reviews statistics grants (more on that presently!).

We begin with a brief history (abstracted from the NIH Web site, *www.nih.gov*). After a humble start in 1887 as a one-room Laboratory of Hygiene with a budget of around $300, today's NIH comprises 27 separate components, mainly Institutes and Centers, and has an annual budget of around $20 billion. Among the more well known institutes are Cancer; Allergy and Infectious Diseases; and Heart, Lung and Blood, to name just a couple of the largest ones. Most of the offices of the NIH are headquartered just outside Washington DC, in Bethesda and Rockville, Maryland. The National Institute of Environmental Health Research is an exception, located in Research Triangle Park, North Carolina. The NIH supports biomedical research through both intra- and extramural programs. Intramural research is that done by scientists employed by the various institutes within NIH. The bulk of the NIH budget (83 percent for fiscal year 2000) goes into its extramural programs, which fund researchers at various universities and research institutions throughout the United States, and even internationally.

Choosing What to Write

The NIH supports biomedical research through many different kinds of grant mechanisms. Sometimes, individual institutes or centers might issue an "RFA" (Request for Applications) or a "PA" (Program Announcement) to address specific issues that are of high priority for that institute (see *http://grants.nih.gov/grants/guide/rfa-files/index.html* for a listing). Although RFAs and PAs targeting statistical methods are relatively rare, some will express interest in methodological issues that might include statistical methods. For example, the National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS) has a PA entitled "Statistical Methods in HIV/AIDS Research" (see *http://grants.nih.gov/grants/guide/pa-files/PA-02-024.html*). So-called "RO1s" (researcher initiated grants) are the most common mechanism used by NIH to fund individuals to pursue their own research ideas. NIH accepts new RO1 applications three times a year (February 1, June 1, and October 1). There are several other mechanisms worth considering, depending on your particular situation. For example, R15 grants (or AREA grants) are designed to support research by faculty located in institutions that have not been major recipients of NIH research grant funds. AREA grants are required to involve undergraduate students as well. The R03 grant mechanism is worth consideration as means of obtaining limited, short-term funding to enable you to pursue a project tht could then lead to a more full scale proposal.

Although we will discuss the grant review process in much more detail presently, it is useful to talk about the general review process now, since this will have a large influence on how you decide to focus your proposal. All applications are processed through the Center for Scientific Review (CSR) and receive a careful initial screening to ensure that practical requirements have been met (e.g., page limits, font sizes, required forms, signatures, and budgetary information). Once successfully through this step, grants receive two critically important assignments. One is to an institute that will fund the grant, should it pass the rigorous standard of peer review, the other is to a "study section" which will provide the independent peer review to assess the scientific quality of the proposal. In general, institute and study section assignments are quite separate. A particular study section will review the scientific merit of grants that have a common disciplinary theme, but that may have a variety of different institutional assignments. Presently, we'll talk about the specific study sections where most statistical methods grants are reviewed. The assigned institute uses the outcome of the study section to decide whether or not to fund the proposal.

There are several things that an investigator can do to influence the critically important institute and study section assignments. For example, it is a good idea to include a cover letter requesting assignment to a specific institute and/or study section. It is also very important to choose an appropriate title for the proposal and to write a clear, concise abstract that allows a reader to immediately get a sense of the proposal. It helps to do some detective work ahead of time to identify an institute that might be interested in your proposal. Because biostatistical method is a relatively small and specialized field, it will often take some time and effort to identify the appropriate target for your application. Although more theoretical or general applications may sometimes be funded by the National Institute of General Medical Sciences, your proposal will generally have the best chance of success if it focuses on the development and application of statistical methods of direct relevance to one or possibly two institutes. For example, someone interested in working on sequential methods for clinical trials might choose to target their proposal toward applications in cancer, in which case the National Cancer Institute would be a natural funding source. Alternatively, a focus on AIDS clinical trials might draw the interest of the National Institute of Allergy and Infectious Disease. Choosing the general focus for your proposal is a critically important first step. It is a good idea to talk to colleagues in your department about how their work is funded. Attending workshops such as the ones sponsored recently by ENAR[1] provides another opportunity to get good feedback on how to frame your research proposal. It is a good idea to check the Web sites of potential institutes to identify current areas of priority, and to make contact with the project officers who work in the extramural research divisions of those institutes to talk about your ideas and to get feedback. Project officers will often be willing to look over a draft proposal and can provide valuable advice about strategies to enhance your proposal's likelihood for funding. If a project officer is aware of your proposal sufficiently ahead of time (at least 3 weeks or so) and is potentially interested in funding it, he/she can submit an ARA (Awaiting Receipt of Application) to CSR through the institute/center referral officer to steer the application straight to his/her program. Most of the institutes have very helpful Web sites that provide helpful tips for would-be grantees, including contact information for appropriate project officers. A list of such sites can be found at *http://grants.nih.gov/grants/grant_tips.html*, or select "institutes" from the NIH homepage, then follow links related to grants and funding.

Writing the Proposal

Once you have decided on the general focus for your proposal, you should start planning the details of the proposal. Assuming that you already have an active research program under way, you should allow at least 6 months of relatively focused effort to put your first proposal together. NIH has strict guidelines on how your grant should be formatted. Well ahead of time, you should download the required forms (PHS398) and instructions from *http://grants.nih.gov/grants/forms.htm* and familiarize yourself with the guidelines. For example, you must include all required sections, adhere to page limits, and use clear, readily legible fonts that satisfy strict minimum size requirements (letter heights not smaller than 10 point; type density no more than 15 characters per inch; no more than six lines of type within a vertical inch). Some of the required sections (including your Face Page, Project Description, Key Personnel, Table of Contents, Budgets, and Biographical Sketches for key personnel) need to be filled out on the PHS398 forms themselves (fillable versions can be downloaded from the NIH site). While it is important to have all the administrative details correct, the two most important parts of your proposal are your Project Description (this must fit inside the box on page 2 of PHS398) and your "Research Plan." The Project Description should succinctly summarize your proposal in such a way that a non-specialist could gain a clear sense of what you will do and why it is important. This short write-up provides you with an opportunity to catch the attention and interest of reviewers and to convince them that something exciting is coming along. Having a well-written Project Description is also important because it may be used by staff in the Center for Scientific Review to assign your proposal to a study section and institute. If your proposal is funded, the Project Description will be made publicly available as well. The research plan must take no more than 25 pages (including tables, graphs, figures) and contains the following sections:

■ **Specific Aims:** This is the place where you outline the list of concrete problems that you plan to tackle. In my opinion, it is a good idea to arrange your specific aims into three to five main groups, with each one containing two or three related, specific subaims. Ideally, the specific aims should fit on a single page and you should establish here a numbering system that will be used throughout the proposal. For example, Specific Aim 3b will always refer to your plan to develop goodness of fit tests for random effects models for ordered categorical data. It is a good idea to mention here any data sets that will be used.

■ **Background and Significance:** This section of your proposal should convince the reviewer that the problems listed in your specific aims section are strongly grounded in and motivated by important issues in health sciences research. You must convince reviewers that by accomplishing those aims, you will contribute significantly to the advancement of biomedical research. This section also needs to convince reviewers that you know the literature and that your specific aims have not been already accomplished by someone else! Hence, it is important to include the appropriate references in this section. It is a good idea to start the section off with a general overview of your broad area of interest. For example, if your proposal is to tackle a variety of statistical problems that arise in longitudinal studies of aging, start off your Background and Significance section with a paragraph explaining why research on aging is important. As you then work your way through the motivation for each of your specific aims and subaims, try to keep a consistent numbering system. Remember, an important goal is to make your proposal as readable as possible for reviewers. You want your aims and logic to be clearly articulated all the way through. You should provide some details about the applications that motivate your proposed research, along with data sets that will be used in your work. Referring to letters of support from subject matter specialists will generally be very helpful.

■ **Preliminary Results:** This is often a slightly difficult section for statisticians to write, since unlike our lab science colleagues, we don't normally collect pilot data to help develop and support our research hypotheses. Many people use this section to describe the background experience of the principal investigator and other key personnel, outlining any key papers or results that might serve as the basis for the methods to be developed if the grant is funded. It's a good idea to list some relevant publications—these will help convince reviewers that you are well qualified to accomplish your research aims. Up to 10 reprints can be included in an appendix. If you are a new investigator, you will not be expected to have a long list of publications yet, but you should definitely describe any relevant ones that you have, including those submitted for publication. Although it will usually be natural for new investigators to continue working on topics related to their doctoral work, reviewers will be looking for signs that the applicant is becoming independently creative, and perhaps moving in some new directions. This section can also be used to describe applied work or data analysis that has served as the motivation for the proposed methodological research. In a proposal to renew an existing grant (a "competing renewal"), this section should also contain a progress report, outlining how well you have accomplished the goals of the previous submission.

■ **Methods:** This section is the meat of the proposal, where you have a chance to describe in detail what you want to do. To the extent possible without sacrificing coherency, the methods section of your proposal should not overlap at all with the Background and Significance section or the Preliminary Results section of your proposal. If, as you write this section, you find yourself starting to justify why the methods are important, ask yourself whether this material should be moved into the Background and Significance section. Using the same numbering system as used in your previous sections to denote different specific aims and subaims, the Methods section of your grant proposal should immediately start laying out the details of how you will formulate your models, solve your equations, compute variances, calculate efficiencies, etc. The emphasis should be on concrete details regarding what you plan to do. For example, if you will do some simulations, describe the models you will use and the conditions you will consider, along with how you will interpret your results. You don't have to have every detail worked out (if you did, you wouldn't need the grant!). But, you need to convince the reviewer that you have the general strategy worked out. If you are proposing a new approach to handling a problem, it will usually be a good idea to outline some plans to compare your approach with existing methods. Many people find that a good strategy is to provide detailed descriptions for the first few specific aims and subaims (perhaps the strongest ones), then have only the broad steps outlined for the others. Reviewers are used to the fact that some aims will be better developed than others. It is usually a good idea to describe your strongest aims first. In general, detail is the name of the game for the Methods section. But it needs to be the right kind of detail. Concentrate on presenting details about what you will do. Excessive detail on background materials will not usually be helpful.

Maintaining a clear, simple writing style throughout the proposal is an essential ingredient for success. As you write, keep in mind the goal of making the grant as easy as possible for reviewers to understand and appreciate. While the importance of clear writing cannot be overemphasized, the most important determinant of success will be the nature of the proposed research itself. There is a fine line to walk in deciding on your general focus and specific aims. On the one hand, you want to demonstrate creativity by tackling unusual or nonstandard problems. On the other hand, you want to tackle problems that you can realistically solve, given your background and expertise. In general, it will be a good idea to write a grant on a topic you are very familiar with. If you are not confident that an idea is a good one, don't include it as a major aim! Tackling methodological problems that arise from consulting or project work is often an ideal solution. Reviewers will generally have a favorable impression of a proposal that demonstrates a sound knowledge of the underlying scientific questions. Balancing theory and application is generally very important. While it is good to propose research problems that are statistically interesting and innovative, reviewers will not be convinced of their importance unless you can also argue for the practical importance of what you are proposing to do.

After you have completed a solid draft of your proposal, have some of your colleagues read it. It is especially helpful to ask the advice of senior colleagues who have successfully applied for their own grants or served as reviewers on study sections. You should aim to have this review occur at least four to six weeks prior to the submission date in order to allow time to fix any problems that emerge. While the proposal is being reviewed, you can focus on more practical details such as working on the budget, obtaining human subjects approval if needed, and gathering appendix materials, and including letters of support. Note that in recent years, NIH has become much more stringent in its human subjects requirements. Your best strategy will be to check with your grants management office or with an NIH project officer well in advance to determine how to address this issue in your proposal.

Budget

You should start thinking about budget well ahead of the submission due date. Most departments will have a financial administrator who can help you with preparing the needed numbers and documentation. You will need to think through the percent effort you wish to devote to the grant yourself, along with the percent efforts of any coinvestigators, associated computing and other expenses, the grant start date, and its duration. These decisions help to determine the "direct costs," for your application. Your grants administrator will then figure out the "indirect costs" which are generally a percentage of the direct costs that go to your school or research institution to help pay for the resources that you need to do your work (your office, heat, administration, etc). Mid-level and senior investigators typically apply for around 30 percent annual effort for themselves for a 3-year period. Faculty who are paid on a 9-month basis might ask for summer salary. While some applicants request 5 years of funding, there is a certain risk in doing so, since the proposed research agenda will need to be particularly strong in order to justify such a long period of support. It is common to request funds for a statistical coinvestigator (say at 20 percent effort), along with a postdoctoral fellow and/or a graduate student. More senior investigators might request salary support for a more junior colleague. Often, it is a good idea to include a subject matter collaborator for, say, 5 percent effort, especially if your proposal is strongly grounded in applications. For example, a proposal focused on statistical methods for cancer clinical trials might include as a coinvestigator an oncologist who would provide data and subject matter advice. Again, it is important that the level of personnel support requested be commensurate with the proposed research agenda. More junior investigators, particularly those applying for their first grant, will typically ask for less in terms of postdoc or junior colleague support, but usually request a larger proportion of their own salary (40 or 50 percent is common for first-time applicants). A few years ago, there was a grant mechanism in place called the FIRST award (R29), which was specifically designed to support new investigators in their transition toward becoming independent researchers. The FIRST awards provided 50 percent salary support for 5 years. While this funding mechanism no longer exists, reviewers tend to think of this model when evaluating proposals from first-time applicants. NOTE: if you are indeed a first-time applicant, make sure you check off the "new investigator" box on the face page of your application. Fortunately, preparing an NIH budget has become much simpler in the last few years because of the NIH's increasing use of so-called "modular grants." Basically, any grant application with a total direct cost of less than $250,000 per year can use the new "modular grant" format. This means that you do not have to provide many details about the budget, and funds can be requested in increments of $25,000. A typical, basic statistical methods grant will have an annual direct cost of between $75,000 and $125,000. More complex interdisciplinary grants involving medical co-investigators will generally be more expensive.

What are some of the other things you can request in your budget? Many people ask for consultant expenses. Usually, this will be a relatively modest amount (less than $5,000), which will enable you to invite a colleague to visit you and work on one of the specific aims outlined in your proposal. As indicated above, reviewers often like to see the involvement of a consultant who is a subject matter specialist. Your NIH budget can be used to purchase needed equipment. For most statisticians, equipment translates to computers! It is reasonable for your budget to include funds for "supplies," as well as travel funds for yourself and perhaps one co-investigator to attend one meeting each year (the current NIH standard is $1,200 per meeting). Once again, submitting a modular grant has the major advantage that you don't need to provide a detailed budget justification, but instead only outline it in broad terms.

The NIH Review Process

So how does the review process work? For many years, most biostatistical grants were reviewed in a so-called "special study section" that focused specifically on statistical methods grants. Several years ago, the Center for Scientific Review undertook a major reorganization of its study sections. One goal of the reorganization was to get rid of the many special study sections and to streamline the review process to more effectively reflect the increasingly interdisciplinary nature of biomedical research. Because the number of biostatistical grants submitted does not warrant the establishment of its own study section, it was decided that biostatistical grants would be reviewed in the Social Sciences, Nursing, Epidemiology, and Methods [SNEM-5] Study Section. According to the NIH Web site, SNEM-5 "reviews applications that focus primarily upon advancing techniques and technologies that address important statistical and mathematical problems, research design and methodological issues, and the modeling of phenomena relevant to biomedical, behavioral, and scientific research. *SNEM-5 reviews generic methodological research that can improve the validity, reliability, or precision of measures; the development of statistical theory and mathematical models to analyze data, clinical trial intervention studies, and nonbehavioral basic science; statistical research targeted at data structures developed in clinical trials; advanced ways of using computers and/or new testing technology, or computational modeling techniques with existing data sets; or applying techniques from other disciplines [e.g., genetics, neurology, computer science] to behavioral and social science topics, as well as other biomedical areas of research. The emphasis and main focus of applications should be upon the methods, statistics, or modeling techniques."* SNEM-5 is still a fairly new study section and is still having its slate of permanent members defined. Ann Hardy is the Scientific Review Administrator for SNEM-5 (see the end of this article for her contact information). Although most statistics grants are reviewed in SNEM-5, there are several other specialized study sections where statistics grants can be reviewed (for example, grants focused on statistical methods for AIDS research).

Study sections generally meet three times a year to review proposals. Reviewers receive the packet of grants to be considered, along with specific assignments to review a subset (usually five or six) in detail. Reviewers will need to declare themselves in conflict of interest for applications from anyone from their same institution or from any close colleague. Reviewers prepare a written critique of each assigned proposal, evaluating each one according to the following:

Significance and impact: Is the work important? If successfully accomplished, will the proposed research have important impact on biomedical science? Reviewers will be influenced by how well you have written your background and significance section in preparing this part of their report.

Approach: Is the planned approach reasonable and likely to lead to success? Has the applicant considered all the possible pitfalls, etc.? The reviewer will be paying close attention to what you have outlined in your methods section.

Investigator: Is (are) the principal investigator(s) well qualified to accomplish the proposed research? Do they have the required training and track record? The reviewers will be paying close attention to your Biosketch(es) and also to the preliminary aims section of your proposal.

Innovation: Is the proposed work new? Creative?

Budget: Is the budget reasonable relative to the work to be accomplished? Is the length of time requested appropriate?

Usually, each proposal will be assigned a primary, secondary, and tertiary reviewer. At the study section meeting, each reviewer will read or summarize the main points of their review. The study section will then have some open discussion of your proposal, followed by scoring. Possible scores range from 100 (perfect) to 500. While scores are assigned primarily on the basis of scientific merit, reviewers will take account of the applicant's background—for example, being a little easier on new investigators (this is why it is so important to check off the new investigator box if you are eligible to do so!). Scores are assigned a percentile that is then used by the various institutes in making their funding decisions. The method of assigning percentiles varies according to study section. In SNEM-5, grants are percentiled on the basis of scores received by other grants renewed in SNEM-5 in the current and two previous cycles. The relationship between percentiles and funding decisions varies considerably by institute, and depends largely on budgetary issues specific to each institute and its own individual funding priorities. As a general rule, however, scores between 100 and 150 are considered to be outstanding and have a very high chance of funding, regardless of institute. Scores between 150 and 200 are often considered to be in a "gray zone" where funding is uncertain. Sometimes an institute will fund a grant that is just above its funding cutoff in terms of percentile, if it is in an area of particularly high scientific priority. Scores of 200 or more will rarely be funded. The process by which reviewers assign scores is hard to describe. In general, I think it is fair to say that people assign scores by keeping in mind these rough guidelines on how scores translate to funding decisions. If three reviewers all independently give very similar scores, that is reassuring to the rest of the committee and the final score will generally be similar. If the three reviewers start out with very different scores, then considerable discussion might be needed before the committee feels comfortable voting on a particular application.

Approximately 4 or 5 months after the initial submission of your proposal, you will receive the written review of your proposal, along with your priority score. These written reviews are often mysteriously referred to as "pink sheets" by the old timers, presumably reflecting days long ago when the reviews actually came on pink paper! If your score is below 150, you can cautiously break out the champagne. If the score is higher than 150, but below 200, you can still have some hope of funding, but realistically, you should start to think about a resubmission. Proposals considered to fall unto the lower half of those reviewed will typically be "unscored." If you get a bad score or are "unscored" for your first submission, don't despair. It happens to most people. Give yourself a week or two to get over your disappointment, then start to carefully evaluate your critiques. Try to determine whether or not the reviewers think that your proposal shows promise and can be fixed easily. Talking to a senior colleague can be very helpful at this stage. If you decide to fix the application and re-apply, respond explicitly to each criticism and suggestion, indicating how and where you have revised your application. This response should be clearly laid out in a section called "Introduction" as described in the instructions to the PHS398 form. If you disagree with the reviewer on certain points, state your arguments in a logical manner, but avoid criticizing the reviewer—this tactic is likely to backfire on you! Add any additional improvements that you have thought of yourself, and point these out as well. It can often be useful to highlight revisions to the proposal itself by using a different font or italics. The more you can convince reviewers that you have responded thoroughly and thoughtfully to the previous critique, the greater your chance of success on your resubmission. Note that you will have only two opportunities to resubmit a grant. After that, it will need to be considered a new proposal.

Conclusions

Writing a grant sounds like a lot of work, and it is. However, even if your grant is not successful the first time, the effort is not wasted. Many people describe the experience of grant writing as a positive one. It is an opportunity to think through your own research priorities and to focus your thoughts. For many people, writing the grant is an integral part of doing the research itself. In some ways, you can even think of a grant as a compilation of a series of half or three-quarter written papers. The Background and Significance section contains the introductions to the various papers, while the Methods section contains an incomplete draft, in outline form, of the main results of the papers.

Winning your first RO1 grant can be the first step in a long-term, satisfying relationship with NIH. Your Project Officer is there to help and advise you. So long as you accomplish your aims, publish your work, and generate new ideas for each successive renewal, there is no reason why your RO1 grant can't stay with you throughout your whole career. During your earlier years, you might be the one doing all the calculations and programming needed to work out the problems outlined in your proposal. As you become more senior, the problems outlined in your grant can be shared with your students and junior colleagues. Eventually, you will be guiding fresh new investigators in how to apply for their own grants!

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[1] *ENAR's first Young Investigator Workshop was organized by Drs. Xihong Lin and Marie Davidian and held at the March 2001 Spring Meetings in Charlotte, NC. Grant writing was a major focus of the workshop. NIH funding has been obtained to support similar workshops for the Spring Meetings in 2002 through 2004. Further details may be obtained by contacting the ENAR business office (www.enar.org).* ■