

■ SPECIAL ARTICLE

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Writing Successful Research Proposals for Medical Science

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HIGH-QUALITY research proposals are required to obtain funds for the basic and clinical sciences. In this era of diminishing revenues, the ability to compete successfully for peer-reviewed research money is essential to create and maintain scientific programs. Ideally, the essentials of "grantsmanship" are learned through observation and participation in grant preparation, but the training environment experienced by most physicians typically focuses on clinical skills. Most physicians are never exposed to a research environment and therefore do not learn how to write grants. The result is that many clinical studies, even when designed by skilled clinicians and those that address important clinical questions, often do not compete successfully with proposals written by basic scientists. This creates a perception that clinical studies are not favorably viewed by research review com-

mittees. The opposite is probably closer to the truth; research review committees are very keen to fund excellent clinical research. Although greater numbers of researchers with Ph.D. degrees have applied for National Institutes of Health (NIH) grants compared with researchers with M.D. degrees over the last 10 yr, funding rates (percent applications funded) have remained approximately the same for these investigators (fig. 1; 1995 success rates: all degrees, 6,759 [26.8%]; M.D.-Ph.D., 370 [23.1%]; M.D., 1,518 [28.1%]; Ph.D., 4,746 [26.8%]; other degree, 125 [23.1%]).§

Capable medical researchers ultimately write research proposals for funding by the NIH. Standards of excellence for NIH grants are high (only the top ≈20% of grants are funded). Research questions posed must be hypothesis driven; the investigator must be qualified to perform the study; and preliminary evidence should be presented demonstrating that the research is feasible and will answer the questions posed. The goal of this article is to review important elements of successful research proposals, with emphasis on funding sources available to the anesthesiology community. Two important anesthesia-specific organizations exist to support anesthesia research—The Foundation for Anesthesia Education and Research (FAER, an organization under the auspices of the American Society of Anesthesiologists) and the International Anesthesiology Research Society (IARS).

Successful applications for research support from FAER and IARS have many of the characteristics of grants funded by the NIH and other peer-reviewed funding sources. These characteristics include (1) a highly qualified investigator(s); (2) for junior investigators, a mentor with a successful track record in scientific investigation, peer-reviewed funding, and mentorship of fellows and faculty; (3) a supportive academic environment; and (4) a scientifically sound proposal. Each of these characteristics is discussed in the subsequent sections.

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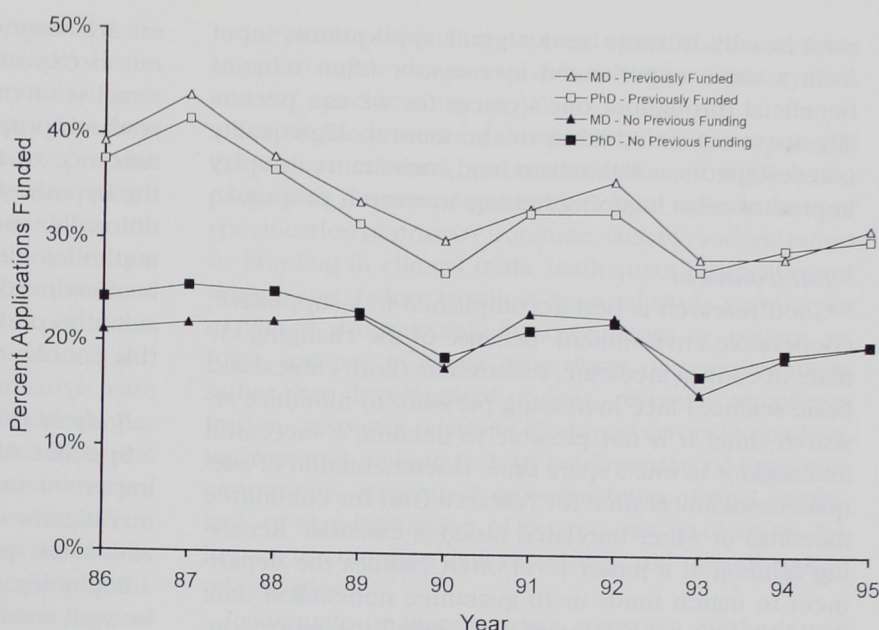
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§ NIH Extramural Data and Trends, Fiscal Years 1986-1995. Bethesda, Office of Reports and Analysis (component of the Office of Extramural Research), National Institutes of Health. (Published on-line and periodically updated. <http://www.nih.gov/grants/award/award.htm>).

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Fig. 1. Overall success rates for NIH funding of scientific applications, 1986–1995. No difference in funding rate is observed between applicants holding M.D. versus Ph.D. degrees. As the success rate for first-time applications was 11.3% in 1993, it is apparent that resubmission of a revised application significantly increases the overall chance of having research proposal ultimately funded.[§]



Preparation of the Investigator for a Proposal

Training of the Investigator

One of the most important components of a successful research proposal is a well-trained investigator. Training in clinical anesthesia is not training in research methodology or scientific thinking; it does not prepare an individual for a career in investigation. Although obvious for basic science research, clinical research also requires commitment of a minimum of 1 yr of dedicated training with a good mentor, and more typically 2–3 yr in the field of the proposed research. The applicant also needs to demonstrate commitment to a career in investigation. Several years of scientific training is the first demonstration of such commitment. Research proposals must document institutional support for nonclinical time, and the investigator must provide evidence that this time has been used wisely and will continue to be dedicated to the proposed research.

The research proposal must document a track record of productivity by the investigator. This expectation increases as the training and career of the investigator progresses. Fellowship awards do not have an expectation of prior research training, so publications from prior research are not expected. At the fellowship level, outstanding letters of recommendation, undergraduate

and medical school performance, and related accomplishments are most important. Because previous training is not required of the fellowship applicant, prior success of the mentor (publications and track record with previous trainees) weighs heavily in the fellowship review. For junior faculty, peer-reviewed publications are expected from the fellowship period. Young Investigator Awards (from FAER) and several new IARS awards require several years as a successful junior faculty member, so expectations of demonstrated research success are further increased. The investigator must demonstrate (1) rigorous training, (2) commitment to research, (3) an appropriate career path, and (4) a track record of productive work. None of these are trivial issues, and none can be easily accomplished without making a commitment to research early in the academic career.

Mentor

The quality of the mentor is another important aspect of awards granted to fellows and junior faculty. Identification of a mentor is explicitly required for FAER and certain junior level NIH grant applications. First and foremost, the mentor must be a successful investigator. Criteria for this include a track record of publication in the area of the proposed research, continued peer-reviewed funding, and a history of successfully training young investigators. Although mentorship is not consid-

ered heavily in more senior grant applications, input from a more experienced investigator often remains beneficial throughout one's career (as we can personally attest to). In addition to the mentor, high-quality coinvestigators, collaborators, and consultants also play important roles in strengthening a research proposal.

Environment

Good research is best accomplished in a supportive, cooperative environment. Because of the changing climate of clinical medicine, researchers (both clinical and basic science) face increasing pressure to minimize research time. It is not possible to become a successful investigator in one's spare time. Documentation of adequate nonclinical time for research (not for committee meetings or other unrelated tasks) is essential. Receiving funding at a junior level often enables the department to match funds or to guarantee nonclinical time to the budding investigator. In general, the more nonclinical time available to an investigator, the more competitive the application.

Other important elements of the environment include people, space, and institutional resources. People include mentors, consultants who can help with specific methodologies, statistical support, helpful colleagues, experienced technicians, a clinical research team, and a dedicated chairperson. There must be adequate space for performing the proposed studies, office space for research personnel, and storage space for equipment and supplies. Institutional resources include related departmental and interdepartmental seminar series, a critical mass of investigators in a related area, instrument development and repair shops, and necessary laboratory space and common facilities.

The Research Proposal

Criteria for a sound research proposal are the same whether the proposal is submitted to NIH, FAER, IARS, or other funding sources. In crafting a proposal, it is essential to consider the perspective of the reviewer; therefore, items of interest to the reviewer are listed after general definition of the grant proposal.

Abstract

Review committees receive dozens of grants. NIH study sections may review as many as 150 proposals during one session. Typically, only two or three review-

ers are assigned to read each grant in detail, but everyone is expected to read each abstract. Hence, the abstract is often one of the most important parts of the research proposal. The abstract should address the significance of the question and the overall topic, state the hypothesis, and point out key preliminary data. Additionally, the abstract should provide a synopsis of methodologies planned. In the end, the reviewer must be convinced that the applicant is uniquely (or ideally) suited to undertake this important study by the end of this concise paragraph.

Body of the Grant

Specific Aims. The specific aims section is critically important in a scientific proposal. It is here that the investigator crystallizes the overall goal of the research and states specific hypotheses.

Beginning with the specific aims, the proposal must be well written and logically organized. A poorly organized grant application is difficult to review, even if the science is otherwise excellent. Typically, the specific aims begin with a short introduction (one paragraph), followed by a formally stated hypothesis. The hypothesis must be answerable by the research methods proposed. Generally, two or three specific aims are outlined with subheadings where appropriate. Organization of the specific aims is often temporal, starting with a proposed mechanism or the first set of studies in a clinical project. In general, the specific aims section should be no longer than one page.

Background and Significance. The background section provides an opportunity to bring reviewers up to date on current research in the area of the proposal. This section should summarize succinctly studies from the literature and related work published by the investigator. The most crucial aspect of the background is to build a case for significance of the proposed research regarding the ultimate clinical application or mechanistic understanding. Ideally, the background section should demonstrate that the current proposal is a logical extension of previous studies in the field and will provide new information and novel insights. In general, the background section should be about one fourth of the length of the grant proposal.

Preliminary Data. Preliminary data provide the opportunity for the investigator to demonstrate his or her ability to perform the proposed research. The goal in presenting preliminary data is to convince the reviewer that the investigator is capable of performing the pro-

posed studies and that the mechanisms proposed are plausible. Good preliminary data support novel (or even unlikely) hypotheses. Each experimental method proposed should be accompanied by preliminary data demonstrating facility and expertise with related preparations. For example, if the investigator proposes using a specific electrophysiologic technique to study an ion channel, evidence demonstrating that this technique has been used by the investigator with other ion channels and a figure showing results from pilot experiments on the channel of interest would suffice. In clinical studies, demonstration of a working investigative team and the ability to enroll a given number of patients per week is helpful. Figures or tables help to convey the message in a succinct manner. They also conserve space in the proposal and create a more impressive effect. Although it is best if the applicant has generated his or her own preliminary data, for training awards, preliminary data from the mentor's laboratory is entirely appropriate. An effective way to organize preliminary data is to present it in the same order as the specific aims (e.g., C.1 preliminary data corresponds to A.1 specific aims, C.2 preliminary data corresponds to A.2 specific aims, *etc.*). Presentation of preliminary data usually takes about one fourth to one third of the length of the grant application.

Methods. The methods are the guts of the research proposal. Unfortunately, many investigators run out of steam by the time they reach the methods, leaving reviewers unconvinced by the proposed methodology. Ideally, the model being investigated should be broken down into simple, logical components, each accompanied by a description of specific experiments/interventions to be performed. The investigator should assume that at least one reviewer is an expert in each method presented. Therefore, enough detail should be provided to convince an expert that the experiment or technique is being performed properly. Methods presented as a list of recipes, requiring the reviewer to guess which method applies to each study, are recipes for disaster. Individual experimental techniques should be state of the art. In addition, approaching a problem from several angles is often helpful. "Lingo" of the field should be avoided; it is very annoying to reviewers to have to look up unexplained abbreviations or to have models alluded to rather than described. For training grants, methods should involve techniques currently being performed in the laboratory of the mentor. An effective way to organize the methods section is to follow the same

order as the preliminary data and specific aims sections (e.g., D.1 methods corresponds to C.1 preliminary data and A.1 specific aims, *etc.*).

The methods sections should include a description of the design, conduct, and analysis of each study being proposed. Common errors in design include lack of specification of primary outcome, lack of randomization or blinding in clinical trials, inadequate justification of sample size, failure to adjust the total study number for expected dropouts/failed experiments or patient refusal, and use of single drug doses or concentrations rather than development of dose-response or concentration-response relations. Common errors in conducting research include lack of confirmation of drug concentrations, inadequate reproducibility of final results, lack of standardization of procedures, inadequate follow-up, incomplete data recording, and overall lack of organization.

Inadequate or inappropriate statistical methods can be a major weakness of a grant proposal. Many investigators feel confident with all aspects of their methods except the statistical section. Because statistical issues underlie the design and analysis strategy for every study, the input of a biostatistician is essential in planning the research and writing the grant application. Statistical considerations include specification of the primary end points that drive power calculations. Common statistical errors in research proposals include lack of sample size/power calculations, treating continuous variables as dichotomous, repeated *t* tests when a more comprehensive modeling approach should be taken, application of statistical tests that assume normality without verifying assumptions, failure to consider covariate effects, and failure to distinguish between interindividual and intraindividual variability. The investigator should be familiar with the concept of statistical power and be prepared to estimate some of the quantities needed to formulate an alternative hypothesis appropriately. The statistical analysis should be clearly outlined with specific methodology directed toward the hypotheses of the study. A statistical reviewer is unlikely to be convinced by a statement that "appropriate statistical methodology will be used" or by a barrage of nonspecific statistical jargon. At least one full paragraph (and sometimes an entire page) of the research proposal should be devoted to statistical analysis. Often several smaller statistics sections are appropriately included after each method is presented.

Even the best methods have potential problems and

weaknesses. It is critical that the methods section discuss potential problems that may be encountered during the study and state how the investigator proposes to deal with these problems creatively. Reviewers tend to be impressed when the investigator presents potential problems that never occurred to them, because it suggests that the investigator is an expert in this area of research. A time line and organizational plan (who will be responsible for what) should also be included in the methods section so the reviewers can determine whether the investigator is being realistic in his or her approach. The methods section is typically one third to one half of the length of the entire grant proposal.

Introduction to Revised Application. Because so few grant applications are funded on their first submission (11.5% in 1993), the new investigator should not be unduly alarmed if his or her application is not funded. When a grant application has been unsuccessful, an investigator should revise the application and reapply, even if the original score was "noncompetitive" (meaning the grant was in the lower 50% of applications). Often the reviewers suggest key changes that will improve the application significantly. When submitting a revised application, an introduction (placed before the specific aims section) is used to discuss how criticisms of the original grant have been addressed in the revised proposal. Because the reviewer's comments are intended to be helpful, it is important to address each concern carefully in the revised proposal (changed text should be highlighted in the revised application by italic, bold, or identifying lines in the margin), with changes outlined in the introduction section. Angry responses to reviewers do not facilitate funding of the revised application. Remember that reviewers usually have a copy of the prior review, and they expect corrections or, when appropriate, an explanation of why you have chosen not to incorporate some suggestions from a prior review. Time taken to revise an application is well spent; as figure 1 demonstrates, investigators who persist in revising and resubmitting their applications

have an increased chance ($\approx 20\%$ with no previous NIH support, $\approx 35\%$ if previously funded) of ultimately being funded.[§]

Insights into the Reviewer's Perspective

In writing a research grant, it is helpful to consider the reviewer's perspective. Key features considered by reviewers include significance, approach, and feasibility. It is wise for the investigator to reread his or her application before submission with these features in mind. The NIH recently has published two documents on-line that discuss review criteria; examination of these documents before submission of a research proposal may prove helpful. These include the Report of the Committee on Rating Grant Applications^{||} and Review Criteria for Rating Unsolicited Research Grants.[#]

Significance

First and foremost, is the investigator asking an important question? There are two general ways research studies can be significant. The first is to demonstrate clinical significance. The litmus test for clinical significance is whether the proposed research will improve patient care. The second is elucidation of fundamental mechanisms underlying disease or biologic processes. The ideal research question succeeds in being significant in both areas.

Approach

The reviewer assesses whether the research plan can support or refute the stated hypothesis. In addition, the reviewer assesses whether the methodologies used provide adequate or, better yet, elegant approaches to the problem. Recently, the NIH has mandated an increasing emphasis on innovation in research.^{1**}

Review committees generally are composed of individuals with expertise in many scientific areas. Additionally, study sections often retain outside reviewers with expertise in the proposed research area. The investigator should assume that his or her methods will be critiqued by at least one expert. Therefore, the investigator should not propose a method that would strike the world's expert in the field as being simplistic, inappropriate, or nonsensical, because the world's expert just might be one of the reviewers. Conversely, some reviewers do not have expertise in the proposed area of research. To ensure that the nonexpert is convinced of

^{||} Report of the Committee on Rating Grant Applications. Revised 5/17/96. Bethesda, National Institutes of Health. (Published on-line. <http://www.nih.gov/grants/peer/rga.pdf>).

[#] Review Criteria for Rating Unsolicited Research Grants. NIH Guide, Vol. 26, No. 22, 6/27/97. Bethesda, National Institutes of Health. (Published on-line. <http://www.nih.gov/grants/guide/1997/97.06.27/notice-review-criter9.html>).

^{**} Brown KS: A winning strategy for grant application: Focus on impact. *The Scientist* 1997; April 8:13-4

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the validity and importance of proposed methodologies, the overall proposal should be written with a logical flow of ideas that build from basic to sophisticated concepts. Beginning each portion of the methods section with a short introduction for the nonexpert, followed by a more detailed description of the proposed methods, is an effective strategy to address the needs of both expert and nonexpert reviewers.

Feasibility

The investigator must convince reviewers that the chosen approach is feasible. Preliminary data provide the best demonstration of feasibility. Feasibility is often demonstrated by a track record of publications or peer-reviewed grant support for the applicant or mentor using the proposed experimental approach. Feasibility also can be demonstrated by appropriate statistical analysis of the proposal. For example, a power analysis and corresponding data on the number of patients with the required characteristics at the investigator's institution helps convince reviewers that a clinical study is feasible.

Anesthesiology Funding Sources

Funding for research performed by anesthesiologists is available from many sources. Because the discipline of anesthesiology overlaps many other fields, anesthesiologists have the opportunity to apply for research funds from agencies as diverse as the American Academy of Pediatrics, American Cancer Society, American Heart Association (national and local), American Thoracic Society, American Society for Regional Anesthesiology, critical care societies, Department of Veterans Affairs, National Science Foundation, Shriners, Society for Cardiovascular Anesthesiology, Society for Obstet-

Table 1. Number of Recipients of NIH Research Project Awards

	1995*
Number of awards	24,039
Number of investigators	18,896
Awards per investigator	1.272
% of investigators with:	
1 award	78.0
2 awards	17.7
3 awards	3.4
4 awards	0.7
5 awards	0.1

* Data obtained from reference 1.

Table 2. Potential Funding Sources*

Fellowship Level	
FAER	Anesthesia Research Fellowship Award (these are often sponsored by a specific component society within the ASA)
NIH	F32 (Postdoctoral fellowships) K08 Mentored clinical scientist development award K01 Mentored research scientist development award Minority Supplements to Mentor's RO1 Award
AHA	AHA Fellowship Award (national and local)
Other	American Lung Association Research Training Fellowships American Thoracic Society Fellowship Fellowships sponsored by ASRA Howard Hughes Research Fellowship Awards National Science Foundation Graduate Research Fellowships and Postdoctoral Awards Numerous private foundations (information available via grants and contracts at most academic institutions) SCA Fellowship Awards SOAP/Braun Fellowship
Junior Faculty Level	
FAER	Anesthesiology New Investigator Award Anesthesiology Patient Safety Foundation Awards Clinical Research Starter Grant Research Starter Grant Young Investigator Award
IARS	Frontiers in Clinical Research Frontiers in Research (basic science)
NIH	R29 (First Independent Research Support and Transition Awards) R01 (Independent Investigator Awards)
AHA	Grant-in-Aid (national and local)
VA	Merit Awards
Other	American Cancer Society American Lung Association Clinical Research Grants Career Investigator Awards Dalsemer Research Scholar Award Fogarty International Research Collaboration Awards Local seed money from the department or medical school Numerous private foundations (information available via grants and contracts at most academic institutions) Robert Wood Johnson Health Care Financing and Organization Grants

* Not an exhaustive list. Abbreviations for organizations sponsoring research can be found in the text.

rics and Perinatology, National Aeronautics and Space Aviation, NIH, and many other private foundations. Grants from FAER and IARS are available specifically to the anesthesiology community.

Table 3. Grant/Training Resources on the WWW*

Biomedical Grants on the Internet
http://www.biomed.lib.umn.edu/grantstext.html
Ellen Barrett's Hints for Writing Successful NIH Grants
http://chroma.med.miami.edu/research/Ellens_how_to.html
Fedex Seminars on Grant Writing
http://www.rams-fie.com/seminars
Foundation for Anesthesiology Education and Research (FAER)
http://www.asahq.org/faer/homepage.html
General Grant Links and Information (anesthesiology)
http://cos.gdb.org/repos/fund/
http://www-personal.umich.edu/~trinket/Resources_for_Grant.html
http://pkpd.icon.palo-alto.med.va.gov/grants/grants.htm
NIH Division of Research Grants
http://www.nih.gov
http://www.nih.gov/grants/training/training.htm
http://www.nih.gov/grants/peer/rga.pdf
http://www.nih.gov/grants/guide/1997/97.06.27/notice-review-criter9.html
Who's Who in Federal Grants Management
http://www.os.dhhs.gov/progorg/grantsnet/whoswho.html

* Not an exhaustive list.

It is important that anesthesiologists continue to apply for NIH grants. For fiscal year 1996, the NIH awarded 149 research grants (including career development grants, R29, R01, and program project grants) to departments of anesthesiology, totaling \$21 million in direct costs (\approx \$31 million in total costs). Because of the diversity of research projects in anesthesiology, these grants were awarded by 14 different institutes, centers, and divisions within the NIH. In analyzing data for three recent review sessions (June 1996, October 1996, and February 1997) from the surgery, anesthesiology, and trauma study section, 26% of anesthesiology applications scored in the top 20th percentile, and 31% scored in the top 25th percentile; clearly no bias exists against anesthesiology in this predominantly surgical study section, at least in this limited sample (Alison Cole, anesthesiology representative for the National Institute of Gen-

eral Medicine Science at the NIH, personal communication, December, 1997).

A brief list of funding opportunities available to anesthesiologists early in their career is shown in table 2. Several sites are available on the World Wide Web (table 3) to facilitate access to grant/training resources for anesthesiologists. We have created an additional website (<http://pkpd.icon.palo-alto.med.va.gov/grants/grants.htm>), which provides access to more comprehensive lists of funding agencies and direct links to funding sources. This website also contains example grants designed to illustrate the grant writing principles discussed in this article.

Conclusions

Successful grant applications require a well-trained investigator who carefully outlines a hypothesis-driven research proposal. Unique to FAER and IARS research committees is that the reviewers are mostly investigators and practicing anesthesiologists. These reviewers fully appreciate the importance of clinical research and enthusiastically support high-quality clinical studies. Although descriptive clinical studies are interesting to practicing clinicians, from a scientific perspective, clinical research must be driven by testable hypotheses. Without a testable hypothesis, clinical research cannot pass the test of adequate significance required for funding.

It is our hope that by demystifying the grant writing and review process that more anesthesiologists will be encouraged to submit proposals for research funding. As part of this effort, we strongly encourage residents and fellows interested in research careers to obtain adequate research training and to apply for appropriate fellowship/junior faculty awards early in their careers.

Reference

1. Marshall M: NIH plans peer-review overhaul. *Science* 1997; 276:888-9