TIPS TO AVOID ANNOYING THE REVIEWERS

Timothy M. Wright, Ph.D.

Think about the reviewer's workload

- 80 applications to review three times a year
- 16 personal assignments - proposals the reviewer must read and be prepared to discuss
- 6 reviews to write, each three to four pages (single-spaced)
- 4 weeks to get it all done
- 2 days away from home and the office
- 1 big pain in the ___!!!

Make the reviewer's job as easy as possible

- A good reviewer approaches every application wanting to support it
- You need to convince the reviewer to be your advocate
- "You never get a second chance to make a first impression"
  - Neatness counts
  - Follow instructions
- Write for a qualified scientist in a somewhat related field
- Don't require backtracking; if you follow the instructions, your proposal will read as a continuous story covering all the basics of what you propose to do and why you want to do it

The reviewer doesn't want to have to second guess your intentions

- Begin with the hypotheses or research questions presented in the "Specific Aims" section; be clear and succinct and be sure to distinguish correctly between hypotheses and specific aims Do not pose self-evident or trivial hypotheses ("we hypothesize that we will find a relationship between bone mineral density and strength")
- A reviewer may not have time to and should not have to study your application; a good tip is to ask a colleague who is not totally familiar with your work to read your proposal before submitting it and see if she understands it
- Write clearly, accurately, and concisely

The reviewer doesn't have time to read the appendices or go to the library

- Provide the entire story in a clear, concise manner in the Research Plan
- Do not rely on appendices or references for any important aspects of your proposal, such as key preliminary results or important aspects of your experimental methods

At study section

- Reviewers not assigned your application probably haven't read it prior to the meeting
- Instead, while your proposal is being discussed by the assigned reviewers, others glance at:
  - Abstract
  - Specific Aims/Hypotheses
  - Budget & budget justification

    - Biographical sketches
    - Letters of support/collaboration
- So don't take any of these sections lightly; they are as important as the Research Plan

Revised applications

- Interpret the summary statement carefully to be sure you understand the reviewers' concerns
- Avoid sarcasm and insults in writing the Introduction to your revised application
    - "They totally misunderstood..."
    - "They clearly don't know..."
- Highlight changes inthe simplest form; perhaps a vertical line in the margin along side new or altered sections of the application, instead of multiple highlights (e.g., don't use multiple means); it's much easier on the reviewer's eyes than reading paragraphs of bold, italicized, underlined text

Pet Peeves

- The "hide and seek" hypothesis; do not bury the statement of your main hypothesis in the text of the Specific Aims page; draw attention to it by white space, bullets, or bolding.
- Too many specific aims; try to limit the number of aims to 2-4 (record in personal experience: 14!)
- The "here's everything I know" Background section; present only the most salient points in composing an argument that will make the case that your proposal will add significantly to our current understanding about a clinically relevant problem
- The "here's everything I've done" Preliminary Studies section; present only preliminary studies that support your proposal as the logical next step in a progression to testing your hypotheses
- Small font sizes (even though 10 is allowed by NIH, it is very hard on the eyes; besides, most reviewers believe you should be able to present your argument in size 12 font in the pages allowed).
- Lack of white space; format your text so that it is not too dense; use blank lines and margins effectively
- Compartmentalization - Part IA2bi, etc.; too many subsections of subsections of subsections increases the chance that the reviewer will lose your train of thought
- If you didn't read it, then why should I?
    - Typographical errors and misspellings.
    - Incomplete sentences
    - Incorrect citations
    - Inconsistent format, font, or heading styles
- Acronyms, abbreviations, and jargon are confusing; they don't save much space and they often lead to confusion on the part of the reviewer
- Figures that are unintelligible (illegible?), usually because they are too reduced in size
    - The unreadable caption
    - Is it a datum point or is it a smudge?

Successful Proposals

- An idea with IMPACT (Significance and Innovation)
- Focused hypotheses
- Reasonable specific aims that are directly related to the hypotheses
- Seductive preliminary studies (not too much, not too little, but just the right amount)
- Innovative, appropriate methods
- Clear path to strong conclusions
- Reasonable budget

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Hypothesis/Question/Specific aims

Richard A. Brand, M.D.

"Entia non sunt multiplicanda praeter necessitatem" ("The number of entities used to explain phenomena should not be increased unnecessarily")

Occam's Razor
William of Ockham (ca. 1280-1349)

The Hypothesis

The basis for any grant proposal lies in the hypothesis(es) or question(s). Evaluation of the proposal begins with the reasonableness of the hypothesis1 . That is, there must be clear logic supporting the hypothesis and any hypothesis must be clearly and unambiguously addressable or any question clearly and unambiguously answerable by the methods proposed.

William of Ockham (Ockegem) taught us to seek the simplest explanation consistent with observations. As a means to predict behavior, Occam's razor often applies in the physical sciences. One need only consider the example of Newtonian physics which predicts astonishingly well for phenomenon except at the speed of light and at the level of atomic particles. But in biology, which Elsasser notes is "unfathomably complex," [Elsasser, 1991] simple explanations rarely suffice owing to the almost inevitably elaborate chains of (causal) physical or chemical reactions underlying all biological responses. Simplistic explanations abound in the surgical sciences, yet we should still strive for the most simple explanations consistent with observations.

Any hypothesis should be supported by clear rationale. This can take the form of sound and substantive experimental observation or data, logical argument, or consensus of opinion in the literature (roughly in decreasing order of plausibility). The reader should have no question the hypothesis makes sense.

On the other hand, one should not propose a hypothesis which makes so much sense (that is, there is overwhelming evidentiary support) it becomes trivial. Popper distinguished "high" and "low informative content" hypotheses. The latter were almost certainly supportable, while the former were not. We learned little, he argued, from low informative content hypotheses. The high informative content hypotheses demand a far greater level of creativity since they are more likely to reflect novel explanations. From these we learn far more (not to mention making a proposal more exciting to reviewers).

No hypothesis is testable, and no question is answerable unless it is posed in terms of (independent and dependent) variables proposed in the experimental design. A well formulated hypothesis will imply an experimental design and vice versa.

Sometimes more or less subtle differences in wording of a hypothesis will make the difference in whether it is important and whether it is testable by the methods proposed.

Specific Aims

The first page should contain the essence of the entire proposal. That is, it should provide: 1.) a rationale, 2.) clear, unambiguous, testable hypotheses or questions, 3.) specific aims to include general methods. A logical rationale and hypotheses or aims need take only two or three paragraphs; specific aims immediately follow.

The beginning paragraph should set the stage by saying precisely why the study is important. This should go beyond "to increase understanding…" a vague remark at best. State exactly how understanding will change the way we think about a scientific problem, the way we explain biological behavior, or the way we would change clinical practices (e.g., medical interventions, screening, prevention),

A second paragraph should provide sentence-by-sentence logic (imagine Aristotelian syllogisms: if 1, 2, and 3, then we logically and necessarily conclude 4 - 4 being the hypothesis). 1, 2, and 3 may consist of bulk of past opinion, or pure logic, or past observations or data. The stronger the source, the stronger the support for your hypothesis(es). All questions or hypotheses should be formulated in terms of independent and valid dependent measures (else they are not testable). You may or may not choose to provide citations in this section, but if you do, they should be brief (they will appear in Background and Significance).

A third paragraph may connect the hypothesis to your specific aims.

Each specific aim should logically follow the major hypothesis(es). Often these aims will be predictions of the hypothesis (e.g., the bending of light by Einstein's Special Theory of Relativity - later demonstrated). Other times they will directly address the hypothesis. Briefly describe the experimental design in one or two sentences, including independent and dependent variables.

Minimize specific aims: 2-4 major aims suffices in most cases, and more may become, or at least appear intractable or impractical.

Formulate "parallel" specific aims in which one does not depend upon the others. Avoid "serial" or "contingent" specific aims in which the second or third or fourth aims depend upon an earlier one: if the first one fails, the others fail.

TIPS

- Limit Specific Aims to one page.
- Formulate no more than four Specific Aims.
- Draft and complete the Specific Aims page as the first task.

AVOID

- Specific Aims formulated as "To quantify…" or "To describe…" Quantifying or describing is a means to an end, not an end. Insure you describe the "end."
- Proposing superficial "goals or objectives"
- Obvious statements of fact: "We hypothesize we can develop a model to…" One can always develop models. The questions are whether they address meaningful issues and can be confirmed.

1Throughout this document, I will use the term "hypothesis" to imply an explanation of some observed phenomenon in Nature. I could equally use the terms "theory," "view," "explanation," "question," nearly interchangeably and without implying or intending any hierarchy. When I use the term "hypothesis," presume the comments equally apply to "question."

BACKGROUND AND SIGNIFICANCE

Richard A. Brand & Dennis R. Clohisy

This section in essence amplifies the first two or three paragraphs of the Specific Aims page. The first paragraph should document the general problem is important: common, costly, troublesome, etc. The beginning paragraph should set the stage by saying precisely why the study is important. This should go beyond "to increase understanding…" a vague remark at best. State exactly how understanding will change practices (e.g., medical interventions, screening, prevention).

Subsequent paragraphs should follow the logic outlined in Specific Aims, but should substantially amplify with appropriate citations. All reviews should be representative of a field, although not exhaustive. Avoid a biased presentation of material (a common error since we tend to present information supporting our arguments, not refuting them). (It is often helpful to identify members of a review group to avoid crucial references from those individuals, although no crucial references should be neglected in any case.)

The Background section provides the applicant an opportunity to demonstrate clear and focused knowledge of the topic area relevant to the application. While those who review your application will have obviously some familiarity with your area of research, often the reviewers will not be as expert in the area as you are. Therefore insure you write a clear, reader-friendly (for the informed but "non-expert") description focusing on critical past, present and future issues involved in the research area. Knowledge must be placed within the context of current methodologies and opportunities. This section should detail how you expect this advance to constitute a significant contribution. The reader wants to know what is known in the field that is relevant to your proposal. They do not want to know everything that is known in the field. After describing what is known in reader-friendly terms, it is then your job to point out what is not known, why it is important to know it, and how you will determine what needs to be known.

Throughout the Background section, your writing should logically build towards what your contribution will be. You need to explain to the reader what needs to be done, and how your results will meet that stated need. You are setting the stage for what you expect to contribute.

The Background section should not reflect a comprehensive historical review. Attempts to do so typically leads to loss of focus and do not demonstrate a clear understanding of relevant knowledge. Focus on describing knowledge that is relevant to your proposal while acknowledging the most significant contributions in other laboratories.

Anticipate reviewer criticisms throughout. When you are aware of contradictory information, note that information and make an effective argument why it is not critical (e.g., flawed studies, not directly relevant, etc.). If you cannot make an effective argument, then apparently contradictory information must be considered in your hypotheses or line of thinking.

When the reviewer has completed the Background section, you want to have them feeling as if you had just told them a story: you understand the past, you

understand the present, and because of your ideas, you will improve our knowledge in the future.

TIPS

- Begin all paragraphs with topic sentences.
- Emphasize a specific concept or point with each paragraph (and topic sentence).
- Insure logical flow of paragraphs (and topic sentences).
- Insure hypotheses are stated in the same words throughout the proposal
- Select concept-driven section titles (if used).
- Tell a story.
- Parenthetically refer to figures or tables; this "trick" forces emphasis on the point, not the figure.
  Use only simple illustrations.
  Parenthetically cite literature with author name and year, rather than numbering citations; this requires more space, but lets the reviewer immediately know the source rather than attempting to locate it in the citations. If your proposal is too long to do this, it's too dense! Parenthetic citation of authors also places emphasis of a statement on an idea, not a person (the cited author).
- Cite work of members of the NIH review committee if relevant and appropriate.
- Avoid excessive numbering of sections.
- Use an uncluttered format, with spacing between the paragraphs and a font of sufficient size that it's easy to read.
- Highlight critical points: summarize sections or draw conclusions in italics.
- Consider writing the Background section as the last task in assembling the grant.
- Insure your literature review and citations reflect the literature, rather than presenting a biased view.
- Allow empty lines between sections and some space on the pages around figures.

AVOID

- Justifying a study by vaguely stating, "…to increase our understanding" - be specific.
- Referring to statements as "hypotheses" when they will not be tested - you will confuse the reviewer as to precisely what you are testing and what you are not.
- Making repetitive statements (reviewers are busy and don't like to read the same thing many times).
- Excluding key observations or references (including those of the reviewers).
- Inventing jargon: use plain English and the simplest word possible which accurately conveys
- Making non-substantive statements. These do not lend clarity. Such a statement would include:
  - "Many investigators have studied…" - rather state upfront what they (as a group) concluded.
  - "We found significant differences between…" - rather state you found an increase or decrease and provide levels of statistical significance when appropriate.
  - X was larger than Y but not significantly so…" - rather, once you have determined a level of significance based not merely upon statistics but also biology, conclude X was no different than Y.
- Writing a "dense" grant. Do not pack a grant on every line just to get in more detail. While adequate detail is essential for understanding, eliminate all unnecessary detail.
- Do not try to get around the formatting policies (e.g., page and font sizes). Making the font so small the referee has difficulty reading the grant just to get in more material will NOT endear yourself to the referee.

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PRELIMINARY STUDIES/PROGRESS REPORT

Richard A. Brand

Preliminary Studies

Preliminary Studies serve two purposes: 1.) Amplify critical concepts or data you have generated and to which you have earlier referred in constructing the logic leading to your hypotheses (questions); 2.) Document your technical expertise in critical methods.

In that spirit, it is best to construct subsections according to critical concepts or methods. The following format is helpful: 1.) Sub-section number; 2.) Subsection title a declarative statement of what you want the reviewer to know (i.e., a critical concept in the logic); 3.) References (published papers, abstracts); 4.) A single paragraph outlining the major points. Below is an example of a reader-friendly subsection of Preliminary Studies following this format.

> **3.1 A rapid, trigger-like response occurs in rat calvarial-derived osteoblast cells (RCOB) (Mellitou et al. 1991, 1992; Stanford et al. 1992, 1995c)** RCOB (5000 cells/mm2) strained (Flexercell System, McKeesport, PA) over six days at -1 KPa demonstrated a proliferative trigger-response (17-fold difference) and a rapid phenotypic response (as measured by osteocalcin or OC expression) between only one and four strain applications per day. (One cannot convert from the vacuum units to strain owing to non-uniformity. The lower end of the range is always 0% strain, while the upper end varies from approximately 5%, at -1 KPa, to 25%, at -20 KPa. The averages lie between these extremes. Similar trends are observed for other cell lines (ROS 17/2.8 and MC 3T3-E1) and other markers that have been evaluated (alkaline phosphatase or AP). Additional studies identified other properties of temporal processing, including a refractory period in the levels of membrane-bound AP.

Additional subsections may contain technical descriptions of past approaches relevant to the current work.

Graphical data or observations often succinctly convey many points and provide a visual break for the reviewer, but also consume space. They may be needed to document you have collected the data. Insure the amount of space used conveys an appropriate amount of information.

Progress Report

With a competitive renewal, the Progress Report may be constructed in a manner similar to the Preliminary Studies above, except studies related to the previous grant period should be highlighted (and an appendix provided when appropriate). The findings of a granting period will usually suggest new directions, indicating new logic (often modified from the original) for new hypotheses or questions. The data and publications of the earlier period will then be organized in a fashion to create this new logic. The organization can

be otherwise similar.

TIPS

- One subsection for each critical point.
- Title of each subsection a declarative statement of some critical point.

AVOID

- Avoid making any one section too long.
- Avoid stating, "We are the first to show…" - chances are you are not, and even if you are it appears arrogant.

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RESEARCH DESIGN AND METHODS

Thomas D. Brown

NIH Guidelines specify what should be included in Research Design and Methods:

"Describe the research design and the procedures to be used to accomplish the specific aims of the project."

"Include how the data will be collected, analyzed, and interpreted."

"Describe any new methodology and its advantage over existing methodologies."

"Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims."

"As part of this section, provide a tentative sequence or timetable for the project. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised."

This section is virtually always the largest portion of research plan (13-16 of 25 pages). No design/methodology is air-tight. Reviewers will know this, and upstream it is crucial to get the reviewer on your side. You are likely, in fact, the expert regarding the "nuts & bolts" of your procedures. Therefore you must "teach" the reviewer and convince them what you are doing is appropriate and adequate for the hypotheses or questions. You should write defensively and "cover your bases."

As implied in the NIH-designated title ("Research Design and Methods") this section has two parts: Design and Methods. There are varying ways to organize this section, and no one way fits all studies. With many clinical or experimental studies, an overview of design best appears first. With many technique-dependent studies, and unless "safe science," it is often helpful to explain methods first to prevent reviewer skepticism of the likelihood of success (i.e., nip criticism in the bud). Methodological novelty often equals potent grantsmanship, but insure any new method is properly validated. The more novel the method and the newer the investigator, the more it needs validation. Insure the reviewer knows what new doors your technique will open.

Your design section should include a credible power analysis

where appropriate. The methods section should make clear what data will be capture and why. Include a statistics section, but view statistics as a servant, not a master.

If your study involves human or animal subjects, the study design must include rationale for choice of subjects. For humans this includes issues related to age, gender, minorities, children. Include inclusion/exclusion criteria appropriate for the hypotheses or questions. For animal studies, species and age must be justified.

It helps the reviewer to organize this section according to your Specific Aims. Each sub-section of the Design should suggest how your results will verify or refute the corresponding hypothesis. This helps to maintain reviewer enthusiasm. Avoid a study design contingent upon the result of an earlier experiment.

The role of any and all collaborations/contracts should be clear in this section. In general avoid off-site collaborations except when essential to completion of the proposal.

Graphics compactly convey a lot of information, provide a visual break for the reviewer, illustrate actual data capture, and "extends the scoreboard" for preliminary work. On the other hand, they occupy space and often reproduce poorly on reviewers' copies. Therefore it is important to use graphics judiciously.

Consider adding a final subsection on potential difficulties and limitations. Consider what issues you would raise were you a reviewer. Be forthright, but don't do the reviewers' work. Restrict it to things they're likely to note. Put serious thought into rebuttals of limitations. Devise credible work-arounds and fall-backs.

TIPS

- Insure a logical path consistent with Specific Aims.
- Provide sufficient detail that:
- Your mastery of the protocol is unquestionable
- The reviewer understands the rationale for trade-offs
- The variables being measured are clearly identified
- The data from the apparatus/assay/model are accurate, reliable & reproducible.
- The necessary logistical arrangements are feasible.
- Get colleague opinion(s) re: burden of proof.
- Keep sentences and paragraphs manageable.
- Cite supporting references, critically, in context and by investigator name.
- Provide context-specific methodological rationale.
- Provide context-specific expectations of working data.
- Walk an assumed sympathetic reviewer step by step through your experiment or model.
- Be positive and confident, but not arrogant.
- Care about your techniques for their own sake.
- Help the research community advance the state of the art.
- Personalize support letters.

AVOID

- Avoid an overambitious proposal; young investigators often attempt too much to make the proposal appear a "bargain."
- Avoid dense, extensive, cook-book protocols.

HOW TO PRESENT STATISTICS IN THE RESEARCH PLAN

Elizabeth R. Myers

Your major goal when presenting statistics in the Research Plan is to describe how the analysis will answer the research question. This is your chance to show the reviewer that you understand how to use the data to answer your question (test your hypothesis). You should also give enough information so that a reviewer can evaluate the statistical approach, and you should justify the number of subjects/specimens for projects involving human or non-human animal experimentation.

Statistics can be presented as a separate section toward the end of the Research Plan (with a title such as "Data Analysis") or as recurring sections under the methods for each specific aim ("Data Analysis for Aim 1," "Data Analysis for Aim 2," etc.). In addition to a section on "Data Analysis," a separate section on "Number of Subjects" can be helpful for the reviewer.

Section on Data Analysis:

For studies that involve descriptive statistics, you should list the variables to be summarized and the procedures for summarizing the dataset. Typical procedures used to summarize a dataset include calculating the mean, standard deviation, frequency, or percentage.

For studies that rely on analytical statistics, you should list separately the major independent and dependent variables ("independent" variables are those factors either controlled by the investigator or chosen as predicting variables in an observational study; "dependent" variables characterize response or outcome). Describe the appropriate statistical approach, which is typically hypothesis testing or confidence interval estimation. Do not forget details such as the alpha level (the probability of concluding that there is an association when in reality there is no association) and the basic assumptions of the statistical approach. Supply a reference if the statistical approach is not well known. Provide the name of the computer program to be used for managing data and performing statistical tests. It is also important to discuss alternatives to your proposed statistical approach if assumptions of the test are violated.

At the end of the section on Data Analysis, try to close the loop by giving a brief interpretation of anticipated results. This interpretation is particularly valuable for complicated study designs.

Section on Number of Subjects:

This section is crucial for any study proposing to use human subjects or non-human animals. You must illustrate that enough data will be collected to support the proposed analysis.

A determination of sample size is also called a power analysis. In essence, you are describing the results of a previously performed power analysis in this section of your grant application. Therefore, you must state all assumptions, values, and methods that went into the power analysis. Then you must state the results.

First, describe the variable (or variables) that was used as the primary dependent variable in the power analysis. In multi-factorial studies, it is also important to power the study on the dependence of that primary outcome variable on the independent factor considered central to answering the research question. For example, if you propose to investigate the differential response of women versus men to a therapy, you would want to power the study on the interaction term between the two factors of gender and treatment. Reiterate the statistical test you propose to use to analyze the data, and make it clear to the reviewer that you used the formula specific to that particular statistical approach in the power analysis. List the alpha value and beta value (the probability of concluding that there is no association when in reality there is one). Describe the effect size (the degree to which an independent variable has an effect on a dependent variable), and give a good explanation for the scientific importance of the chosen effect size. If you used values for standard deviation or predicted differences from the literature or your own preliminary studies, make this clear. Last, give the results of the power analysis as number of subjects. A table or graph can be an effective way to present the numbers determined for each aim of the study.

You should be aware that a power analysis is a "ball park" estimation. Number of subjects is dependent on alpha, beta, and effect size. Relatively small changes in any of these parameters can have a significant influence on the estimated number required to detect effects. You may want to discuss the limitations of your power analysis if applicable.

It is important to consider the number of subjects for several reasons. Clearly, as both researchers and members of society, we all want to avoid killing animals or testing humans needlessly. With regard to research, you want to enhance the probability that an important effect will be detected. With regard to effective grant writing, you want to demonstrate to the reviewer that you have been careful and methodical in your study design.

TIPS

- Provide enough information for a competent colleague to reproduce the analysis
- Separate the description of statistics from other methods with a header such as "Data Analysis"
    - Describe the major independent and dependent variables
    - Describe the appropriate hypothesis test or interval estimate
    - State statistical hypotheses a priori
    - Give a brief description of how you will interpret the analysis
- Separate the description of the power analysis from

other methods with a header such as "Number of Subjects"
    - Power the study on the dependent variable of primary interest
    - Power the study on the dependence of that variable on the independent variable of primary interest
    - Provide the assumptions and values used in the power analysis
    - Unless you have good reason, use alpha=0.05
    - Use beta £ 4 times alpha
    - Use the formula for the power analysis that corresponds to the specific statistical test proposed under "Data Analysis"
    - Use an effect size that is scientifically important and explain this in the proposal

AVOID

- Proposing overly complicated designs with too many factors
- Giving too much information on statistics (don't give a statistics lecture)
- Proposing an under-powered study
- Using the formula for a t-test to determine the sample size when your study is more complicated than a simple comparison of two groups
- Using an effect size that has little or no clinical or scientific impact

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HUMAN/ANIMAL USE CONSIDERATIONS

Gary Friedlaender

Protection of Human Subjects

It is the purpose of the Human Investigation Committee (HIC) or Institutional Review Board (IRB) to establish and implement policies that: 1.) safeguard the rights and welfare of human subjects; 2.) protect the interests of investigators. This requires: 1.) balancing risks and anticipated benefits; 2.) informed consent; 3.) equitable selection of subjects.

To meet these requirements, one needs a purpose, background, location, duration, research plan (including statistical analysis), economic considerations, and a complete description and justification of the subject population. Issues related to the latter include numbers of subjects, ages, gender, inclusion of minorities, children, special groups (mentally disabled, prisoners, etc). In addition, complete inclusion-exclusion criteria are required.

Risks must be described and assessed and alternatives to the evaluation procedure or intervention (as appropriate) explored. The investigator must demonstrate how risks will be minimized, what treatments will be offered if a complication ensues, and who treats the subjects as well as who pays.

Fully informed consent procedures include how, where, and by whom the study will be conducted. An informed consent form should include a subject information sheet with an invitation to participate, the study purpose, the selection criteria, a description of all procedures involved, the risks and inconveniences to the patient, any benefits to accrue either to the subject or society, economic considerations (such as additional time away from work), and a description of alternative evaluation procedures or treatments. Confidentiality must be insured. Note whether the subject will receive compensation for participation. Finally, the consent must include a statement noting the subject has a right to question all aspects of the study, and there will be no prejudice for treatment if they choose not to participate.

Special explanations or consent forms may be required for children, mentally disabled, prisoners, patients with diseases causing societal prejudice (e.g., HIV).

Animal Welfare

The welfare of animals used in the course of research is usually assured through the oversight of an institutional Animal Care and Use Committee. As with studies involving human subjects there needs to be a complete description of the research plan. However, special consideration must be given to species, age, gender, numbers of animals, anesthesia (terminal and survival experiments), discomfort (survival surgery), hazards, genetic alterations. One must specifically justify the use of animals (as contrasted to in vitro approaches, analytic models, or even humans), the choice of species.

Hazards include infectious and chemical, physical, or irradiation agents. In the case of certain toxic chemicals or radiation materials, waste disposal arrangements must be specified.

Veterinary care must be outlined to include: minimization of discomfort, anesthesia, analgesics, antibiotics. In the case of any study involving animal sacrifice, the methods of euthanasia methods must be provided.

Finally, any federally-funded proposal requires accredited animal care facilities. Housing and any treatment sites (e.g., surgery) must be provided.

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BUDGET

Barbara D. Boyan

Jack L. Lewis

Personnel

Justify each person who will do substantial work on the grant and will get paid on the grant. Be detailed (2-3 lines) in describing duties; show that you have thought about this. Make sure there is someone to perform all needed tasks, and the expertise is included for all more complex tasks. Emphasize special expertise where present.

Remember to pay yourself. As PI you will always design experiments, analyze data, and write manuscripts and reports. Reviewers know this, but do not always know the magnitude of this work, therefore you must tell them. If you anticipate doing technical tasks (e.g., performing surgery, running gels, culturing cells) you should note this. Otherwise, state whom you will supervise. In general a PI will spend 15-25% of his or her time, although there will be exceptions outside of these guidelines.

Today, most science is multi-disciplinary and inter-disciplinary. Your proposal will likely include colleagues that must be paid. Generally, the minimum salary for senior participants is 5%. Anything less will be suspect, suggesting that the person will not really do anything but is being used to make the proposal look good. Senior research associates may be typically included for >25% and postdoctoral Fellows 50 to 100%. Insure they will do what you say they will do and that it actually requires the amount of time you indicate. Study Section accepts the reality of your life: they do not expect your fingers to do the actual work. They do expect post-doctoral fellows to get their hands wet, however.

Consultants

If you need a consultant (or two, or three), you need a consultant. Don't get carried away and do keep your budget request relatively small. Consultants are colleagues who are as committed to the project as you are. Justify, justify, justify. Be sure their letter of commitment

is personalized, strong, and states what contribution they will make to the project. Write it for them (you know what you want), e-mail it to them, and ask them to edit it and print it on letterhead. Remember to include the title of the proposal at the top of the letter or in the text of the letter to relieve Study Section of any concerns that the consultant has never heard of you before.

Equipment

In general major new equipment is budgeted in Year 1 since it ordinarily takes time to purchase, debug, and otherwise become familiar with its use. Ask for what you need, including replacement of current equipment. Consider replacement costs in out-years. But, justify, justify, justify. If you need something big and expensive, be sure that you can't rent time on someone else's equipment, or make it clear that you will use it every day, day after day, for how ever many years you will be in science.

Travel

One trip per year for the PI and co-PI, not to exceed $1,500. If you really live in Timbuktu and advanced purchase econoclass airfare is always >$1,500, prove it in your justification.

Supplies

You have to have them. Ask for enough money to buy what you need, but you must calculate the minimum costs to do what you propose to do (e.g., 3 Ab kits, one set of pipettes, etc.). Costs will change by year 2, but NIH specifies increases for inflation unless you can justify more. Justify expenses for animals. Make a table with number, purchase costs, surgery costs, and housing per diem. Make clear if you divide the costs over several years.

Other Expenses

Research is expensive. Remember to include such items as: publication costs (page charges, color prints, posters, etc.): $2,000, radioactive waste disposal (may be an indirect), ultrapure water, service contracts and routine lab maintenance pro-rated to grant use, dishwashing services, etc. Don't just list, tell why you need them.

Consortium Costs

These may apply to colleagues at different institutions with independent budgets ,colleagues at your institution but in different budget entities (labs, departments, schools, etc.). The same care must be taken in preparing their budget. You must justify the

need for the consortium arrangement and its costs as part of your budget.

Calculating Modules

Once you have gone through the above process, you know approximately what everything will cost. Round up to the nearest $25K and follow the instructions for a modular budget. Justify everything that is out of the ordinary.

*If you take your time constructing your budget, it will match your work plan. Study Section will do the right thing. Of course, the funding agency has the final word! You will be ready.

TIPS

- Be sure to ask for what you really need, not too little and not too much.
- Remember:
  - A study Section can smell a rat.
  - They expect people to be paid because they will be committed.
  - Study section will not support mentors not involved.
- Boyan's Rule:
  - One technical person per 100% FTE.
  - Two technicians per grant is the magic number.
  - This can be more than two humans, but if >2, less than 100% commitments should be used.
- Remember that absolutely nothing will go the way you planned; add a few this-es and that's.

AVOID

- Do not ask for $'s for a department chair that will waft past your office to discuss your project. This person is an unpaid consultant.
- Basing your budget on your lab or institutional needs, such as your salary or support of a tech. Base your budget on what is needed to do the proposed work.

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INTERPRETING THE PINK SHEET

Linda J. Sandell

The "pink sheet"

The NIH scientific review was traditional printed on pink paper and thus the name "pink sheet" was born. It hasn't been pink for a number of years now, but the name seems difficult to erase from the collective unconscious of grantees!

Archaic - what it isn't:

- Not a pink sheet anymore
- Not a summary of the reviews anymore

What it is:

- Compilation of reviews from primary, secondary and, possibly, a third review
- Short summary from the Scientific Review Administrator (SRA)

The following is an example of the first page of the Summary Statement.

If your sheet looks like this, you should be very happy!

JAMES PANAGIS, MD, MPH SUMMARY STATEMENT

301-594-xxxx (Privileged Communication)
Application Number R01 AR99999-

1Review Group:

PATHOBIOCHEMISTRY STUDY SECTION
Meeting Dates: IRG: JUNE 2000 COUNCIL: Sept./Oct 2000
Requested Start Date: 01/01/2001 MONROE,

MARILYN, PH.D.
CEDARS-LEBANON HOSPITAL
LOS ANGELES, CA 28098

Project Title: SIGNAL TRANSDUCTION IN MEN IN POLITICS

IRG Action: Priority Score: 103 Percentile: 2.5
Human Subjects: 10-NO HUMAN SUBJECTS INVOLVED
Animal Subjects: 30 - ANIMLS INV> - VERIFIED, NO IRG CONCERNS

And if not…(that is, you are not in the top 10 percentile units,

I. Read the summary statement quickly
II. Accept only good parts (just kidding)
III. Underline what you CAN fix.
IV. STAR the big problems
V. DO NOT get paranoid - as you have just seen, this is a pretty good process
VI. Gt over it!

The summary statement can be your best council.

Read the reviews carefully

- Is there consistency among reviewers? Be honest
- Remember - a proposal must be better than about 80% of the submitted proposals to be funded - this is a competition

What are the Consistent Comments?

- Proposal too broad
- Proposal too diffuse
- Not enough experimental detail
- Too much experimental detail
- A specific experimental design does not lead to interpretable results

Can these be addressed?

Is there a fatal flaw in the proposal?
For example, if your hypothesis is that BMP-7 is responsible for induction of chondrogenesis in perichondrial cells

And your Preliminary Results fail to demonstrate BMP-7 in or around perichondrium, you really have no basis for your hypothesis.

To guard against these breakdowns in logic (and they happen, amazingly easily), please have others read the proposal at many different times during its development. Breakdown in logic and rationale, difficulty in reading, and naivite can be easily picked up by a more neutral observer.

Does the hypothesis lack novelty?
For example, BMP-2 stimulates bone development.

Or, Inhibition of enzyme activity will delay progression of osteoarthritis.

Where have you been?

Why are the reviewers unenthusiastic?

Often they will tell you quite directly, for example, "The lack of productivity of this investigator lowers the reviewer's enthusiasm for this proposal"

"The lack of a testable hypothesis renders this study a fishing expedition providing descriptive information at best"

Focus you efforts on the main theme criticism (but answer all parts).
The following excepts are real
You want to go from this type of discouraging statement…
"The current grant represents the first resubmission of a proposal evaluated in X, 2001. The previous reviewers had significant enthusiasm for for the topic and the hypotheses proposed. However, the application was criticized for poorly constructed and detailed experimental plans that were insufficiently

supported by preliminary data and were lacking in interpretations of potential results. Serious concerns remain that the sloppiness of the written plan may correlate to imprecision in the actual design and execution of the experiments as well, particularly in newly proposed areas of investigation"To this very positive statement…
"...The grant proposal now represents a well-written, well-organized, hypothesis-based project, that offers an appropriate experimental design, which makes innovative use of sophisticated new analytic methodologies, and live human subjects, describes proper statistical analyses, and is underpinned by solid supporting preliminary data. These positive elements are augmented by the strengths of the principal investigator and his diversified (combined Basic science and clinical) research team, and environment.

The following are a group of hypothetical comments you may experience, please give them some time and consideration and discuss with fellow grantees.

"The experimental plan was extremely difficult to follow."
You would:

"The preliminary data did not support the interpretation."
You would:

"The investigator has no track record."
You would:

Other Information in the Summary Statement

The Program Director will be your contact to the NIAMS

Members of the Study Section
You will not know who reviewed your proposal, but all members of the meeting group should have voted.

BUDGET

Project Year	Direct Costs Requested	Direct Costs Recommended	Estmated Total Cost
1	200,000	200,000	296,000
2	200,000	200,000	296,000
3	200,000	200,000	296,000
4	200,000	200,000	296,000
5	200,000	200,000	296,000
	1,000,000	1,000,000	1,480,000

This is a lot of money!

Resubmission

Introduction to revised grant

- Three pages maximum
- Be very nice and business-like
- Be succinct and hit major points first

Then answer all smaller points:

The proposal will likely have new reviewers - at least one or two, so make sure you are speaking to a broad audience. The are unlikely to bring up new

criticisms unless you give them new targets. They will be most concerned for response to the previous reviewers comments. However, they must review the grant anew taking into account the previous review and your responses. It is possible that new criticisms will arise.

Indicate changes in the body of the proposal

- Underline (no), italics (good), bold (usually no)
- Sidebar (good for large sections)

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GETTING THE FIRST GRANT

Scott A. Rodeo

- Make sure the hypotheses are testable using the methods described.
- In the methods section, relate the experiments very specifically to the hypotheses / specific aims. Give a detailed explanation how the experimental result will support the hypothesis. Don't assume the reviewer's are on the same wavelength as you are. Explicitly state the rationale linking hypothesis to specific experiments.
- Have a logically sequenced order to the experimental design, that is, one part leads to the next to the next etc.
- Anticipate what might go wrong and have back-up plans for what to do - e.g., what will you do if no differences are detected between groups? What would a negative result mean, and how will the study proceed in the light of such a negative result?
- Do not propose development of a new model (if model fails-grant fails).
- Demonstrate that you can do/have done the techniques proposed.
- Try to have some publications in the area of the grant, to show expertise and preliminary data
- Establish collaborations for methodology/techniques for which you do not have expertise. Include experts in field as help. Don't go it alone!
- Have a "mentor" who is part of the grant. Preferably this person is a PhD if you are an MD clinician-scientist.
- Stick to your area of expertise, as demonstrated by preliminary data.
- Carefully write the preliminary information section to demonstrate that you have the ability/resources/experience to carry out the grant.
- Provide good supporting letters.
- As a young investigator, try to convince the reviewer that you are going to be a productive investigator in this area over time. Supporting letters should also make this point.
- Respond carefully to reviewer's comments/criticisms when re-submitting.
- Follow instructions!! (length of each section, etc.).
- Proofread carefully before submitting.
- Consider industry funding and foundation funding for preliminary studies to collect enough data and establish a "track record" of production.
- Review and re-review the grant prior to submitting.
- Have experienced investigators in your department critically review the grant.

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"IL DESTINO DI GRANT APPLICATIONIO" BY GIUSEPPE LINGUINIBR>

(Courtesy, Dr. Timothy Wright)

Cast (in order of vocal appearance):
Alfredo, a professor ..... Baritone
Wu Li, a postdoc ..... Tenor
Kathy, another postdoc ..... Alto
Nicolette, Alfredo's secretary ..... Soprano
Adriana, Alfredo's wife ..... Soprano
Bubba, Alfredo's son ..... Tenor
Julieta, Alfredo's daughter ..... Soprano
Stephano, Scientific Review Administrator ..... Basso
Erminio, another professor..... Basso

Act I, Alfredo's Office:

The curtain rises showing Alfredo sitting in his office with two postdocs, working on a manuscript which has been rejected by Nature. In a dramatic opening aria, they lament the fact that the reviewers found the manuscript unexciting ("I reviewers sono malto stupidi"). Nicolette, the secretary arrives with a box of NIH grant applications for Alfredo to review. Alfredo opens it, and finding only 12 grant applications, rejoices. He is joined by the two postdocs and the secretary in a quartet in which they sing of the virtues of having to review only 12 applications ("Il lighto loado"). Their happiness soon turns to sorrow when Alfredo discovers a note indicating that he is primary reviewer on an additional 18 applications which will arrive at a later date ("Il grande boxo digranti"). The four lament the twist of fate, Murphy's law, and the Peter Principle. Alfredo, realizing that he will have no time to spend with his lab group or family for the next 6 weeks, sadly departs for home carrying the box of applications.

Act II - Scene 1, Alfredo's office:

One month later, Alfredo is still hard at work on the applications, having completed only 4, and these were the short R15 applications. He sings a sad aria, reflecting on the fact that the Scientific Review Administrator wants the triage list the next day ("Il listo di crappo"). Nicolette enters with an envelope from NIH. Alfredo, thinking it contains yet another supplement, tosses it onto a pile, and tries to find his place in the application he was reading. Just then, Wu Li enters with some important data that needs to be published immediately, before the competitors beat them to it. They sing a duet ("La publicazione o il scoopo") in which Alfredo laments that he has no time to help write the manuscript as he really must get through 26 more applications before the meeting next week. Wu Li leaves, and Alfredo returns to the grant application, only to be interrupted by Kathy. She is distraught that she hasn't gotten a raise in the two years since she has been with Alfredo. He promises her a large raise if his own application is funded, explaining that he is waiting for the summary statement ("Il

sheeto pinko"). After their duet, Kathy leaves and Alfredo returns once again to the application. Within a minute, he jumps out of his seat and grabs the envelope he hastily tossed onto his desk, realizing that it is the long-awaited summary statement ("La posta junko o il sheeto pinko").

Trembling, Alfredo tears open the envelope and lets out a cry upon seeing the score, which is clearly not in the fundable range. He sings a moving aria lamenting the lack of sufficient funding for basic science ("Mio granto finito"). Unable to concentrate anymore, Alfredo goes home.

Scene 2, Alfredo's home:

Later that night, Alfredo arrives home. His wife and children are ecstatic that Alfredo has come home before they have gone to sleep. However, their happiness is short-lived as they learn the reason for his surprise homecoming. His family is not sympathetic to the fact that only a small number of people actually get their grant applications funded, and are upset that Alfredo's application was only considered `excellent' not 'outstanding' ("Papa - un nincompoopo"). Disheartened, Alfredo sits down at his desk and begins to read an application. However, just as at work, he can't read for more than a minute until his children or wife interrupt him for something.

This continues for a couple of hours, at which point Alfredo has nearly finished reading an entire page of the application, but unfortunately falls asleep before getting to the next page.

Act III, A Holiday Inn in the Bethesda Valhalla, home of the Gods and Goddesses of the NIH:

The scene opens to reveal a large table surrounded by serious looking me and women. Alfredo is among the mortals, who have been invited to Valhalla to decide the fate of 137 grant applications. At the side of the room are the Gods and Goddesses of NIH, the program officers of the various agencies, dressed in white tunics. They are feeding from a large tray of grapes, and drinking decaf coffee. Stephano, the Scientific Review Administrator begins the meeting with a hour-long aria about the grant review process and the need for confidentiality ("Non asko, non tello"). The first grant application to be reviewed is one with Alfredo as the primary reviewer. Alfredo likes this grant application since it describes an imaginative series of experiments that concern an important but not well studied biological question ("Se succeede, - il Nobel Prizo"). Furthermore, this, application described all of the key points in a single page; the limit of Alfredo's attention span with all of the interruptions he gets. His enthusiasm is countered by the other reviewer in what is probably the most famous aria of the opera ("Non hypothesiso, non preliminary dato"). Other reviewers join in with other comments regarding the lack of independence of the applicant, the lack of feasibility studies, and the general observation that the area must not be very important or else others would be working on it. Finally, the Grants Technical Assistant rises and joins in the singing ("Givmi il floppi disko"). Everybody in the room finally joins in except for the Gods and Goddesses, who have loved from the tray of grapes to a large table filled with melon balls, which they eat with toothpicks, and a man in a Holiday Inn Valhall tunic who is restocking the toothpicks. As it is clear that no new comments have been made for at least 45 minutes, a vote is

finally called for, and in a dramatic moment, Alfredo sings out "1.0" ("Uno"), while the other reviewers vote for a worse score ("Il granto non-competitivo"), finally arriving at a consensus of 2.0. During the aria discussing the score, the man in a Holiday Inn Valhalla tunic becomes noticeably distressed and begins consuming vast quantities of coffee, until he collapses just as the aria ends. One of the NIH Goddesses identifies the man as Erminio, the applicant of the grant that just went down the tubes.

Even though Erminio is fatally poisoned with caffeine, he is still able to sing a moving aria reflecting on the weaknesses of the current grant review system ("Il idioti reviewers screwed-upo"). The opera ends with the reviewers placing Erminio's lifeless body in the boxes under the table and against the walls that hold the discarded grant applications, covering him with glossy photos of his data. As the curtain is being slowly lowered, one of the reviewers comments that it's a good thing the application wasn't given a really bad score, or who knows what the applicant would have done.

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