American College of Surgeons

Surgical Investigators Conference

Grantsmanship Workshop

Group Leaders' Manual

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How to use this manual

This manual is intended to serve as a focus for open discussion among the participants. The role of the Group Leader is to facilitate discussion among the participants. Accordingly, the most important activities of the Group Leader will be to pose questions and promote interactions.

This manual consists of points, questions and scenarios intended to provoke discussion. The questions and scenarios are incomplete in the sense that they do not address all aspects of grantsmanship. Thus, the content of this manual should be regarded as a collection of suggestions with which to organize the session. The manual is not a directive. Group leaders are encouraged to modify and embellish based on the leader's experience and the specific needs of the group.

The success of the workshop depends in part on the enthusiastic participation of the young investigators. While young surgeons are typically extroverted, some may bring specific fears to the workshop. These include (but are not limited to):

- fear of appearing foolish to the group leader
- fear of admitting ignorance in the presence of their peers
- fear of admitting prior failure in the granting process
- fear of later failure in the granting process

These fears may manifest in diverse ways. A few participants may attempt to control the discussion. Others may be reluctant to participate. The group leader should anticipate these behaviors and consider methods to restore balance and flow to the discussion.

This manual is arranged to mirror the structure of typical grant applications. Like the applications themselves, there is an understandable tendency to focus the discussion on the earlier parts of the manual. Like the applications themselves, failure to pace progress through the discussion will result in an incomplete workshop. The participants need to see the importance of distributing their effort through all aspects of their own applications.

Suggested actions are highlighted by underlining. They are suggestions and not directives. Group leaders should feel free to adopt, adapt or reject as appropriate based on the leader's experience and the needs of the group.

Group leaders may wish to post a list of the domains in which applications are evaluated (significance, approach, innovation, investigator, environment) to remind the group of the reviewers' assigned tasks.

Introduction and Introductions

Begin by introducing yourself. Emphasize that the workshop is a "safe haven" or closed forum in which ideas and problems can be freely discussed without fear that honest opinions and concerns will be used in adverse ways. This spirit is similar to the environment of a study section where reviewers must be free to express opinions about applications and even challenge one another. Such a mutually supportive environment of the workshop is an ideal place to share concerns and experiences while developing new skills.

Before inviting the participants to "go around the room" and introduce themselves, consider asking each participant to write down the "theme" of his/her research. Explain that the theme of research is not an hypothesis or a specific aim (those terms to be discussed and defined later) but rather a declaration of the interest and direction ("overarching idea") which each expects to sustain their new laboratory. If they do not yet have their own laboratory and a theme, ask that the participant articulate the theme of their last mentor's lab. Remind participants that a thematic statement is part of every grant application. *The theme should be a single declarative sentence.* Examples might include:

- Metastases arise when tumor cells are deposited in a microenvironment which favors proliferation.
- Multiple organ dysfunction reflects a failure to regulate inflammatory and anti-inflammatory responses to injury.
- Optimal healing of fractures requires load and immobilization.

Ask the participants to introduce themselves and state their research themes.

Consider using two or three themes suggested by the group to start a discussion, illuminating the way in which a too-narrow theme can limit a young investigator while a too-broad theme can give an impression of naïveté and lack of focus.

Specific Aims

Two key strategies are worth stating here and reinforcing through the workshop. First, the NIH and the reviewers expect that the applicant will follow the instructions included in the PHS 398 kit. The instructions are explicit and directive. New investigators are strongly encouraged to contact experienced investigators, the local Gifts and Grants (Grants Management) office of their home institution, and especially their program officer at the NIH to clarify anything in the instructions that is not clear to the applicant. Second, responses to the instructions should mirror the language of the instructions themselves. For example, if an instruction reads "…state the broad objectives…" the simplest response begins, "The broad objectives are…".

Word for word, the hypothesis and specific aims page is probably the most important page in any grant application. Although a grant cannot be earned on the basis of a perfect hypothesis and specific aims page, grants have-—and will continue to be—lost on the basis of mediocre efforts here. The focus of the discussion in the workshop should be on this page of the grant application.

Since each of the participants should have read and/or written several grant applications, consider asking the participants to list what they believe are the critical elements of the hypothesis and specific aims page. It may be easier to phrase the questions as, "By the time *any biomedical scientist* has finished reading your hypothesis and specific aims page, s/he will be able to say that the hypothesis and specific aims are…..:"

Answers might include

- a logical intellectual environment within which to explore the theme of your lab
- complementary, such that completion of the specific aims will substantially support or refute the hypothesis proposed
- focused, such that each experiment that the applicant will propose can be tested for relevance to every specific aim
- achievable, in the sense that a knowledgeable scientist can envision established methods which might be brought to bear in service of each specific aim
- meaningful, such that achievement of the specific aims and testing of the hypothesis will add to biomedical knowledge irrespective of the particular outcome of the experiments

While the "theme" provides an overall direction to the lab, the hypothesis independently frames each grant application. For this reason, hypotheses must be chosen with extreme care and revised to fit the needs of the lab, the resources and talents of the investigator, and the rapidly evolving knowledge of the field.

Consider asking the participants to take a moment and write down hypotheses that

might flow from a familiar-to-all theme (such as “Infection control among surgical patients requires reengineering of clinical practices”). *It is important to choose a familiar-to-all theme to ensure that all participants can contribute.* Consider reading several of the hypotheses and select one which will allow for the development of rational specific aims and one which will not. Consider asking the participants to try to develop specific aims from each. *The purpose of the exercise is to highlight the importance of checking that the hypothesis drives “achievable” aims.*

(Testable hypotheses might include: “Nosocomial infections result from patient-provider-patient contact.” Difficult-to-test hypotheses might include: “Antibiotic usage influences nosocomial infections.”)

Having selected a doable hypothesis and listed half a dozen specific aims, consider telling the participants they must select between 2 and 4 aims, and consider asking the participants to rank the aims and give their reasons for the ranking. *The purpose of the exercise is to recognize that aims which appear “attractive” at first blush may prove unhelpful, undoable and so on. The aims MUST serve the hypothesis.*

Having articulated an hypothesis and listed 2-4 specific aims, the writing must be targeted towards a knowledgeable scientist who is unfamiliar with the area. This means that the ideas must be expressed in simple, declarative sentences avoiding jargon and abbreviations wherever possible and otherwise defining jargon where necessary. More than any other section of the application, the hypothesis and specific aims page must be easily grasped by the reviewer on one or two readings. Clarity counts, simplicity counts.

While creativity in the service of clarity is always encouraged, many experienced scientists use a fairly standard structure that includes three general sections:

- The “setup” paragraph which illuminates the relationship between a pressing problem in biomedicine and the theme of your laboratory
- The “hypothesis” paragraph which points to a specific problem or area and culminates in the statement of the hypothesis
- The “specific aims” paragraph which lists the specific aims and alludes to the techniques to be applied in order to achieve each aim

It is not necessary to write these paragraphs immediately, but experienced investigators --and reviewers-- will eventually test those paragraphs as follows

1. The “setup” paragraph should be transposable into a summary paragraph completing the significance and background section. In other words, it should strongly persuade the reader that the topic is important and worthy of his/her attention.
2. The “hypothesis” paragraph should be transposable to the close of the preliminary data section. In other words, the hypothesis which drives the application needs to follow as the next step logically following what is presented as preliminary data.
3. The “specific aims” paragraph should preview the types and direction of the experiments which will be proposed

Paragraphs which fail these tests should probably be revised to pass. Again the reviewer, consciously or unconsciously, will perform these tests.

In summary, the hypotheses and specific aims page is the first substantive contact the reviewer will have with your ideas. Organization, brevity and a readable structure count for a great deal.

Significance

The knowledgeable reviewer may well skip over this section in your application. However, you should assume that at least one of your assigned reviewers (typically the third reviewer or "reader") will be relatively unfamiliar with the field, much less your work. The applicant writes the significance and background section for this unfamiliar reviewer. The unfamiliar reviewer will be in the weakest position to judge the quality of your preliminary data or the relevance of the research plan. For this reason, the unfamiliar reviewer will unconsciously give enormous weight to the significance and background section. Two points should be made. First, the relevance of the science to clinical medicine and mankind should be clearly stated. This is a strength for surgeon-scientists and may not be apparent to some reviewers. Second, the applicant will be evaluated with respect to currency of knowledge and facility with which that knowledge is integrated into the discussion. Applicants, especially those submitting amended applications, should refresh this section close to the time of (re)submission to ensure that it is up-to-date.

The significance section should address the following questions: Does the project address an important problem or critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatment, services, or preventative interventions that drive this field?

In this section, the applicant is writing a story. It is non-fiction and will describe good science, but it is a story nonetheless. For this section to work effectively on the applicant’s behalf, the applicant should consider what makes a story readable, namely writing which engages the reader, develops the basis for the applicant’s selection of theme, and arrives at a specific point leaving the reader knowing what to expect but hungry for it just the same. Within the context of a story framework, the applicant must demonstrate his mastery of the field’s knowledge. This is usually accomplished through a balanced review that highlights both breakthroughs and unresolved issues.

The writer’s first task is to specifically identify the ending of the story. The ending should be strong enough to leave the reviewer appreciating why the applicant has enthusiasm for his chosen theme. The ending should be sufficiently focused to suggest to the knowledgeable reader several tractable hypotheses, any of which could serve the theme of the lab.

<u>As an exercise, consider asking the participants to write the LAST few (3-4) sentences of a significance and background section in their field of interest. If they are mystified, ask them to identify the major unsolved problem which is driving their particular laboratory interest and to write 3-4 sentences explaining why this major unsolved problem, above all others, is important to them, their colleagues, the patients and to the health of the nation.</u>

Those “last few sentences” drive the story. The elements of the applicant's story are of course individual to the applicant but probably should not deviate too far from conventional wisdom heard in professional meetings and captured in current reviews of the field. The logical elements of "story", however, are fixed. The applicant must select a beginning point (often an historical event in the field such as a critical report or the

proceedings of a major meeting from which a consensus emerged) and demonstrate how scientific questions were subsequently asked and answered. Although such demonstration appears simple, parallel threads must be woven into a coherent whole. The earlier the beginning point, the greater the challenge to the applicant (there's a lot more science to cover), but the greater opportunity for the applicant to demonstrate mastery of the field in a few paragraphs. No matter what the beginning point, the penultimate paragraph in this section should summarize "what is known" so that the final paragraph can illuminate "what is unknown" and eventually justify selection of the specific hypothesis.

(The story should take a familiar, predictable form. The popularity of the "_____ for Dummies" series of books confirms that readers new to any field value a simple approach with plenty of signposts (in the Dummies book series, these are actual signposts—icons--including "tips", "technical stuff", etc.) . As an exercise, new applicants might wish to pick up a few applications well *outside* their expertise and read the significance and background section.)

<u>As an exercise, consider telling the participants to take the following "last few sentences" and list the historical elements they might include in a significance and background section:</u>

"Despite detailed knowledge of the coagulation system, specific risk factors which predispose hospitalized patients to deep venous thrombosis, and identification of effective prophylactic measures, pulmonary embolism remains a leading cause of unexpected morbidity and mortality among surgical patients. The goal of this new laboratory is the reduction of embolism-related morbidity and mortality…"

The point of this exercise is that the content of the significance and background section depends strongly on precisely what hypothesis is to be tested. There is inevitably much more background material than can possibly be included. While the background is a "review", it is a focused review. It must be balanced but is not expected to be comprehensive. It is not possible to start at Virchow and review everything that has been done to present day. Two strategies which could emerge are (1) begin at a recent consensus conference and discuss how new knowledge raises specific questions or (2) start at the beginning but choose a specific thread (for example, heritable predisposition to DVT as a mechanism for developing ideas about genetic contribution to risk, identification and potential interventions).

Remind the participants that two of the five domains of evaluation are "significance" and "approach". Significance is established almost entirely by this section, and the reviewer will form an initial opinion about the sophistication of the applicant's approach based on her review of background.

Innovation

The innovation section should address the following questions: Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches, or methodologies, instrumentation, or interventions proposed?

The preliminary results section is no longer a part of the new short application. However, it is important to provide preliminary data as the canvas on which the applicant displays her ability to organize problems, perform experiments and critically interpret the data. Preliminary data should be included as part of the significance, innovation, or approach section to support these sections.

The most important challenge for the applicant is to logically order the experiments already performed. The logical order is rarely the order in which the experiments were actually performed. The beginning of the section and end of the section are fixed points, but the middle of the section should be ordered so that each experiment adds to what is previously established. Central experiments which advance the science from the theme to the hypothesis should be clearly identified. Often, the applicant can help his/her cause by having the structured presentation of experiments reflect directly upon the structured specific aims. The cause is aided because the reviewer will recognize that the experiments which will ultimately be proposed are not "shotgunned" but rather follow from demonstrated, well-designed experiments.

While a central experiment should suggest an advance, additional subsidiary experiments are typically performed to confirm the advance or to exclude reasonable alternative explanations to the advance. (For example, if a central experiment suggests that a signal is transduced via a particular second messenger system, the additional experiments will likely include both inhibitor studies using a spectrum of mechanistically distinct inhibitors directed at that particular second messenger system as well as inhibitors directed against other potential candidate second messengers.) Subsidiary experiments should be grouped with their central experiments.

Once the experiments have been ordered, the applicant should select a presentation style. There are two general options. One option is to take each central experiment as a section and use the section to describe how each central experiment and the subsidiary experiments inexorably drive towards a particular conclusion. Methods are often embedded in the section to clarify the choice of subsidiary experiments. The second option is to use a more conversational, narrative form which focuses on the flow from theme to hypothesis, embedding entire experiments (methods, controls, data and interpretation) into the figures. The first option is traditional and always acceptable. It may be the safest for the novice investigator. Experienced scientists writing for the most competitive journals are required to exercise the second option. While the second option is seemingly more casual, it is in fact more efficient. The applicant may wish to compare an article appearing in a specialty journal with one which appears in Science or Nature: the latter

is more conversational, but also more compact.

There is a second purpose to the presentation of preliminary data, namely demonstration of specific methods. In order to accomplish the experiments which will eventually be proposed, the applicant must either demonstrate facility with each method or secure and document assistance from another scientist qualified in every undemonstrated method. “Showstopper” methods (methods critical to the application) must not only be demonstrated but evaluated. For example, if the application hinges on surgical thyroidectomy in rats, the applicant will be expected not only to report adequate survival but also to test the animals for the completeness of the thyroidectomy.

Consider asking the participants what they as reviewers would expect as demonstration of “showstopper” methods for applications which involve one or more of the following:

- Administration of an antibody directed against a selectin present on the surface of a leukocyte to prevent a critical step in the inflammatory response
- Transfection of antisense DNA to interrupt a particular cell signaling pathway in a unique cell type.
- Determination of gender dependency of responses in mouse models of transplantation
- Testing the utility of an artificial retina created in vitro by layered cell culture
- Ex vivo stimulation/expansion of tumor infiltrating lymphocyte populations for therapeutic purposes.

Approach

The experiments proposed must flow logically from the specific aims. Nearly all applicants find it helpful to recapitulate the specific aims at the beginning of this section to remind both the writer and the reader of the direction of the application.

Specific aims are rarely if ever achieved by independent experiments. Rather, they are achieved through a central experiment and subsidiary experiments, the latter intended to confirm or exclude potential interpretations of the central experiment. Implicit in this structure are five items critical to each experiment, central or subsidiary:

A. The applicant selects the method most appropriate to the central experiment.
B. The applicant organizes the experiment to confirm that the method is working as anticipated (appropriate controls).
C. The applicant anticipates a particular result and designs the experiment so that it is interpretable with sufficient numbers and appropriate statistics
D. The applicant has an alternative approach if the preferred method does not work
E. The applicant has an alternative direction should the method work but the result appear contrary to prediction

These five items are often named rationale and design, expected results, statistical evaluation, pitfalls, alternatives. The reviewer is sensitized to look for each of these items, and it is especially helpful to flag these items in each experiment by consistent subheadings. Reviewers are not impressed by the numbers of experiments proposed. They are fussy about the details embedded in the five critical items. The elegance of the experiments proposed strongly influence the reviewer's perception of "innovation". The rigor with which these five items are covered is the single most important influence on the reviewer's perception of the "approach". *Every* experiment should be complete with respect to each of the five items.

The applicant is asked to include a timeline. There are two reasons that the timeline is important. First, it provides the applicant with a guide to what resources will be needed at successive times. Second, it provides the reviewer with a "reality check" on resources, time commitment and personnel. Experienced reviewers familiar with the applicant's field will match the description of the experiments to the timeline to determine whether the applicant has a grasp of the reality of ordinary progress.

Once the "experiments proposed" section is written, the applicant should review the list of experiments to determine that either s/he has included preliminary data (or a published manuscript) from his/her lab demonstrating every technique. For each technique not demonstrated, a meaningful letter from a qualified consultant/collaborator indicating the necessary support must be appended to the application.

<u>One of the mistakes young investigators make is to stress "specific methods" rather than "experimental design." Clarify the difference to the group.</u>

Institutional Review/Vertebrate animals/Human subjects

As an exercise, consider asking the participants to describe the mechanisms used by the NIH for assuring appropriate protections where experiments involve rodents (or humans).

Major granting agencies, especially the NIH, are extremely sensitive to protections afforded experimental subjects. Reviewers are REQUIRED by the Congress to evaluate applications with respect to these protections. It is important to realize that confirmation of the relevant protections occurs in two stages.

The relevant institutional committee must review the proposed experimental protocols and (where appropriate) the protections afforded human subjects including consent, oversight and so on. Many novice and experienced applicants believe that this is the only evaluation required and that the application merely restates the approval granted by the relevant institutional committee. This is incorrect.

Once an application is submitted, reviewers are given summaries of the PHS 398 instructions which explicitly outline questions that must be answered and (especially for human subjects) formats that must be followed. These particular instructions regarding human and animal subjects are taken very seriously by the NIH and by the reviewers because these particular instructions are mandated by Congress. Applicants are free to propose any experiments they wish but the experiments must be fully justified if vertebrate (or higher) animals are used. Required justifications include—but are not limited to—selection of a particular species, use of a specific gender, exclusion of age groups and so on. In the case of human subjects, the requirements are tighter still. It is not enough (for example) to say that patients will be drawn from the general hospital population: the PHS 398 instructions require a distribution table indicating gender and racial/ethnic group. It is not adequate to say that a particular ethnic group is underrepresented because your hospital does not care for patients in the group—the exclusion must be justified as scientifically valid. Congress and the NIH do not care about the convenience sample of patients who happen to be in your hospital.

Similarly, Congress requires children to be included in human studies unless a scientifically valid reason for excluding children can be demonstrated. Several valid exclusions are discussed in the PHS 398 instructions.

The bottom line is that while these topics might appear to be "afterthoughts" owing to their placement in the application after the "Research Plan", they require the same care, time and attention as the other parts of the application. Understanding and following the rules is critical to success.

It should be mentioned that these are administrative issues and have no bearing on the score that is voted on the basis of scientific merit. The problem is that applicants who fail to read and follow these instructions to the letter risk having their science deemed highly meritorious (a terrific score) but go unfunded owing to failure to comply with the PHS 398 instructions on animal and human protections.

NIH eSubmission Tips for Investigators

Prepare to Apply - Start early!

Get informed

The new process requires close coordination between investigators and grants administrators. Work with your institution's central grants office early to learn how your institution is managing the new submission process.

Get registered

• All Project Director/Principal Investigators (PD/PIs) listed on an electronic application must have an eRA Commons account with the PI role.

o Work with your organization to get an account set up.

o If you are already an NIH reviewer and have an account to use Internet Assisted Review you still need to work with your institutional official to ensure you also have the PI role.

• Your eRA Commons account will stay with you throughout your career. The same account can be affiliated with multiple institutions.

Ensure you have appropriate software

• Talk to your institution to find out if you will be relying on Grants.gov's forms-based solution or an alternate solution specific to your institution.

• You will need a way to convert your text documents into PDF format. This format is required by NIH for all text attachments to the form.

Find Opportunity and Download Package

• All funding opportunities are posted in the NIH Guide for Grants and Contracts and in Grants.gov Find.

• **IMPORTANT:** All electronic applications must be in response to a funding opportunity announcement (FOA). Application packages are specific to individual FOAs (i.e., can't reuse application forms from one opportunity to another).

•General opportunities have been posted to capture unsolicited, investigator-initiated applications. These announcements have the term "Parent" in the title and can be found on the parent announcement page of the NIH Office of Extramural Research website.

Prepare Application

• Work with your central grants office to determine what parts of the application package you are responsible for completing.

• Develop the research plan and other text documents as usual using a word processing program. Once finished, convert the document into PDF format and split into the required separate documents following the instructions in the research plan section of the SF424 (R&R) application guide. Check the PDF files carefully to ensure graphics and legends, etc. are as intended.

• Follow ALL instructions in the application guide and within the FOA. Instructions in the FOA "trump" those found in the application guide.

• Remember to include your eRA Commons Username in the PD/PI Credential field of the R&R Senior/Key Person Profile component. NIH requires it for application processing, but it is not marked on the form as a Grants.gov mandatory field since it is not needed by other agencies.

• Once your application is received by NIH, our systems automatically generate the table of contents, page numbers, headers and footers. Use section headings in your documents to make sections easy to identify for reviewers.

Submit Application to Grants.gov

• PIs cannot submit the application themselves. Only the Authorized Organization Representative (AOR) can submit applications to Grants.gov.

• Many grants offices are asking for applications early to ensure on-time submission. Check with your grants office for specific instructions on how and when to get your completed application to your AOR for submission.

• Grants.gov does not send any email notifications regarding submission status to the PI, so keep the communication lines open with your grants office.

Check Submission Status in Commons

• NIH provides status emails to the AOR and the PI, but email can be unreliable. Proactively check your application status in eRA Commons. Allow up to 1 weekday from the time NIH has retrieved the application from Grants.gov for the status to appear in eRA Commons.

• The NIH Electronic Submission website and the application guide are excellent resources for resolving errors and warnings.

• Errors are fatal – your application will not be accepted until all errors are resolved and the AOR submits a complete “Changed/Corrected” application through Grants.gov. Warnings do not stop application processing.

Check Assembled Application

• No one cares more about your application than you! After your error-free application is assembled in the eRA Commons you will have two weekdays (excluding federal holidays) to check it – use it! This is your first chance to view/print the application just as a reviewer will see it. Remember, if you cannot view it, we cannot review it! Corrections to the application after this viewing period can only be made through and at the discretion of the Scientific Review Officer (SRO) and will be an addenda (i.e., reviewers will still see your original application submission).