

**STRATEGIES FOR SUCCESS:
HOW TO WRITE A GRANT IN CANCER CAM**

The National Cancer Institute's

**Office of Cancer Complementary and Alternative Medicine
Research Development and Support Program**

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PREFACE

As cancer patients continue to explore alternative treatments and practices, the need for reliable scientific data increases. The National Cancer Institute (NCI) remains devoted to the rigorous investigation of potential treatments and modalities in the prevention and treatment of cancer and its symptoms, whether the source is unconventional or unexpected. Rigorous scientific investigations in Complementary and Alternative Medicine (CAM) can and should be conducted.

Unfortunately, the development of competitive research proposals in cancer CAM and securing federal funding is often challenging. Cancer CAM applications to the National Institutes of Health (NIH) must meet all the general criteria required of any application. In addition, competitive applications are successful at addressing some of the challenges specific to cancer CAM topics.

This document not only compiles information from existing NIH grant writing resources, it highlights some of the issues unique to CAM and CAM related research areas. We have included many of the issues raised by review committees and presents some of the potential solutions for applicants. We hope this is helpful in the preparation of grant proposals to the NCI and to other peer-review funders interested in providing funding support for scientific research in cancer CAM.

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Major Source Documents and Helpful Websites:

Everything You Wanted to Know About the NCI Grants Process...but Were Afraid to Ask.
Prepared by the NCI Grants Administration Branch, NIH Publication No.02-1222, Revised April 2002. <http://www3.cancer.gov/admin/gab/index.htm>

Qualitative Methods in Health Research: Opportunities and Considerations in Application and Review. Office of Behavioral and Social Sciences Research, National Institutes of Health; Bethesda, MD, NIH Publication No. 02-5046, December 2001. <http://obsr.od.nih/Publications/Qualitative.PDF>

Expert Panels in Cancer CAM Research: Developing the State of the Science in Research Methodologies. Expert Opinions on Methodology: Development of Cancer CAM Symptom Research, NCI's Office of Cancer Complementary and Alternative Medicine, National Cancer Institute, Bethesda, MD.

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INTRODUCTION

NCI Organization

The current NCI organizational structure can be seen in Figure 1. Four extramural research divisions, one intramural research division and one intramural research center monitor and administer NCI's cancer-research activities through extramural and intramural research programs. The Office of the Deputy Director for Extramural Science (ODDES), which is part of the Office of the Director, coordinates initiatives across NCI's four extramural research divisions: the Division of Cancer Biology (DCB); the Division of Cancer Control and Population Science (DCCPS); the Division of Cancer Prevention (DCP); and the Division of Cancer Treatment and Diagnosis (DCTD). The Office of Cancer Complementary and Alternative Medicine (OCCAM) is located within the ODDES (see Figure 2). The ODDES also monitors and administers the Centers, Training, and Resources Program, as well as the Center for Health Disparities Research and the grant program supporting minority initiatives.

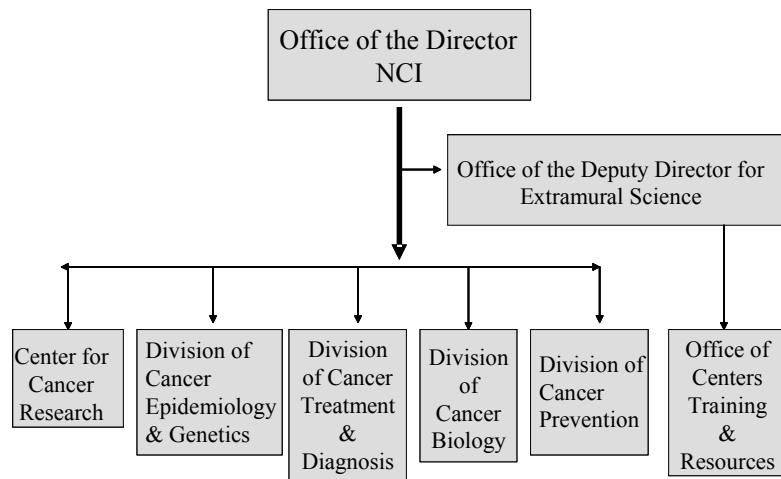


Figure 1. NCI Organizational Structure

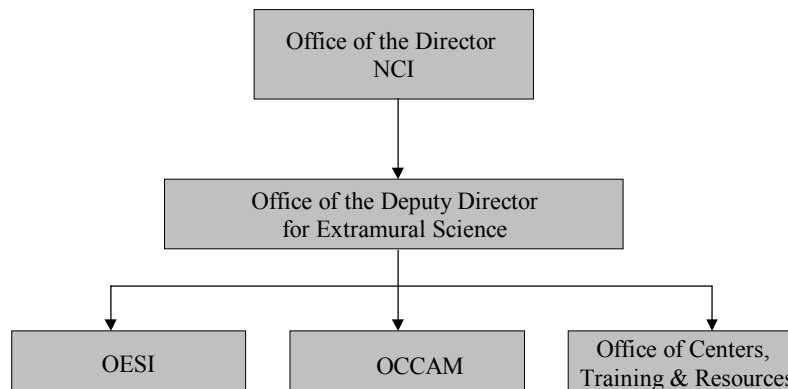


Figure 2. NCI Office of the Director Organizational Structure

NCI Mission

The mission of the NCI is to eliminate cancer and prevent the devastation that cancer imposes on individuals, families, and society as a whole. NCI's goal is to stimulate and support scientific discovery and its application to achieve a future where all cancers are uncommon and easily treated. NCI works toward this goal in two major ways: 1) NCI provides vision to the nation and leadership for NCI-funded researchers across the United States and around the world; and 2) NCI works to ensure that the results of research are used in clinical practice and public-health programs to reduce the burden of cancer for all people. The National Cancer Institute coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients.

NCI's Office of Cancer Complementary and Alternative Medicine

The National Cancer Institute has a long history of interest and support of cancer CAM research. In 1998, the National Cancer Institute established the Office of Cancer Complementary and Alternative Medicine (OCCAM) to support the scientifically rigorous study of CAM modalities as they relate to the diagnosis, prevention, and treatment of cancer and its symptoms. The NCI's OCCAM is committed to developing the foundation for scientifically rigorous research in cancer CAM and symptom management.

A major goal of the OCCAM is to foster the integration of quality cancer CAM research within all appropriate divisions of the NCI. To further this aim, the OCCAM Research Development and Support Program creates initiatives, activities, and funding opportunities to attract, encourage and support the development of scientifically rigorous cancer CAM research.

TYPES OF FUNDING INSTRUMENTS

Using a variety of funding instruments, including contracts, grants, and cooperative agreements, the NCI accomplishes much of its mission through services provided by non-federal entities. Each instrument has a specific purpose and application, thus creating different relationships between the parties.

Contracts

The NCI uses the contract instrument to procure cancer-research services and other resources needed by the federal government. Contracts are used when the principal purpose of the transaction is to acquire a specific service or end product for the direct benefit of, or use by, the NCI.

Grants and Cooperative Agreements

In contrast to contracts, grants and cooperative agreements are federal financial assistance mechanisms used to support and stimulate research. Assistance relationships are established when the principal purpose of the transaction is to transfer money, property, services, or anything of value to a recipient to accomplish a public purpose or to stimulate a particular area of research authorized by law. The two types of assistance mechanisms used by the NCI are the grant and the cooperative agreement.

Grants are used when: 1) no substantial programmatic involvement is anticipated between the NCI and the recipient during the performance of the activities, thus allowing the recipient significant freedom of action in carrying out the research project; and 2) there is no specified service or end product expected for use by the NCI.

Cooperative agreements are used when: 1) the applicant is responding to a specific NCI announcement for cooperative agreements and must tailor the proposal to the announcement's requirements; and 2) substantial programmatic involvement is anticipated between the NCI and the recipient during the performance of the activities.

This document focuses on these assistance mechanisms: grants and cooperative agreements (for more detail, see *Everything You Wanted to Know About the NCI Grants Process...but Were Afraid to Ask* <http://www3.nci.nih.gov/admin/gab/98GPB/98GPBtoc.htm>).

GRANT MECHANISMS AND GRANT ANNOUNCEMENTS

Investigators should be familiar with these terms and how they are used at the NIH. Grant mechanisms refer to the type of research grant while a grant announcement refers to a call for applications for specific types of grant mechanisms.

Grant Mechanisms

Research Project Grants

Research Project Grants are awards for investigator-initiated research proposals. Several types of awards are made in this category, which vary in type of mechanism, type of eligible applicant, total amount of support, and length of time. Fiscal year 2001 research project grant expenditures totaled \$1,696,603,000, accounting for 45.2 percent of the NCI budget. In Fiscal Year 2002, the NCI supported approximately 315 CAM and CAM-related research projects. As of March 2003, the NCI has supported an additional 62 projects.

P01 Research Program Project Grant

Research Program Project Grants (P01s) support an integrated, multi-project research approach involving a number of independent investigators who share knowledge and common resources. A P01 has a defined central research focus involving several disciplines or several aspects of one discipline. Each individual project should contribute to or directly relate to the common theme of the total research effort, thus forming a system of research activities and projects directed toward a well-defined research program goal.

R01 Research Project Grant

Research Project Grants (R01s) support a discrete, specified research project to be performed by the named investigator(s) in an area representing his/her specific interest and competencies. This is generally referred to as a traditional research project grant. R01 proposals in cancer CAM topics may face a challenging review process because these proposals require strong supportive preliminary data. Many cancer CAM research areas lack the kind of preliminary data necessary

to support a competitive R01 proposal. Other mechanisms, such as the R03 and R21, are available to provide funds for pilot and preliminary studies.

R03 Small Research Grant

Small Research Grants (R03s) provide research support specifically limited in time and amount for studies in categorical program areas. Small research grants provide flexibility for initiating studies that are generally for preliminary short-term projects. These grants are non-renewable.

R21 Exploratory/Developmental Grant

Exploratory/Development Grants (R21s) support the development of new research activities in categorical program areas. Support is generally restricted in level of support and time. In cancer CAM research, the R21 is one of the most important available mechanisms because it can be used to support preliminary research proposals. When preparing an R21 proposal, it is important to include some description of how this project fits into an overall research plan and how this project may be developed into a R01 proposal. From the beginning of fiscal year 2002 to March 2003, the NCI has funded or plans to fund 35 R21 proposals. The NCI only accepts applications for R21 grants that are in response to a specific grant announcement.

For a list and detailed information about all NCI grant mechanisms, see Appendix I.

Grant Announcements

The principal investigator (PI) usually initiates an application for a grant. Investigators may send unsolicited proposals (investigator initiated) in response to a specific grant announcement. Under some circumstances, applications will be accepted only when a specific grant announcement is identified.

For new, expanded and/or high-priority programs, the NCI may encourage the submission of grant applications by using the following types of solicitations: Program Announcements (PAs), Program Announcements Reviewed in an Institute (PAR) and Requests for Applications (RFA). Each of these announcements has certain characteristics related to funding and/or review procedures.

Program Announcements (PAs)

PAs describe continuing, new, or expanded program interests for which grant or cooperative agreement applications are invited. Applications in response to PAs are reviewed the same manner as unsolicited grant applications (i.e. by chartered peer review committees of the Center for Scientific Review (CSR) or by NCI Initial Review Groups (IRGs)).

Funds for Program Announcements may or may not be set-aside. Program Announcements with set aside funds are called PASs.

Program Announcements Reviewed in an Institute (PARs) share the same characteristics as PAs with the addition of special referral guidelines and are reviewed by a specific Institute's IRG.

A PA, PAR or PAS will generally have three receipt dates per year and will be open for two years before being considered for renewal.

Requests for Applications (RFAs)

RFAs are issued to invite grant applications in a well-defined scientific area to stimulate activity in NCI programmatic priority areas. A single application receipt date is specified, and the announcement identifies the amount of funds earmarked for the initiative and the number of awards likely to be funded. Applications are evaluated for responsiveness to the RFA before review. Applications received in response to a particular RFA are reviewed by an appropriate NCI IRG or by a special review group.

All PAs and RFAs are published in the NIH Guide for Grants and Contracts (<http://www.nih.gov/grants/guide/index.html>). A list of funding opportunities in cancer CAM can be found on the NCI's Office of Cancer Complementary and Alternative Medicine's website at <http://cancer.gov/cam>.

It is important to note that applications in cancer CAM topics may be appropriate and considered responsive to many NCI announcements that may not necessarily have CAM related language in the title or text. Therefore, announcements list program staff contacts. Applicants are strongly encouraged to contact staff to discuss the appropriateness of a cancer CAM proposal to a specific announcement.

Letters of Intent (LOIs)

Notices of PAs and RFAs will generally indicate dates for Letters of Intent. These letters, though optional, provide useful information for the determination of the potential workload of the review group and for the identification of potential reviewers with relevant expertise. Therefore for CAM applications, the submission of such letters may significantly increase the quality of an application's review.

THE GRANT APPLICATION PROCESS: PREPARATION, DEVELOPMENT, RECEIPT, ASSIGNMENT AND REVIEW

Because it takes approximately nine months from the time an application is received until NCI funding determinations are completed and awards are issued, it is essential for applicants to submit strong and competitive proposals (see Appendix II for details).

Grant Preparation

This is the initial stage of the process. At this point, investigators may have identified the type of research project, how long it would take to accomplish, what level of funding it would require, and the potential team of investigators or expertise needed for its successful completion. Applicants should contact relevant program staff as early in the process as possible. See NCI's website for a listing of program staff <http://www.nci.nih.gov/researchfunding/scientificprograms/>. Program Director contact information is also listed in announcements (RFAs, PAs, etc.), and staff are usually identified by Institute or interest area.

Foreign applications:

Applications from foreign institutions are accepted. However, funding of such applications depends upon whether the topic is relevant to the American public and whether or not there is unique expertise at the foreign institution. Applicants from foreign institutions are strongly encouraged to contact program staff prior to preparation and submission of a grant proposal. Program staff can help identify the funding potential of applications and may be able to suggest potential US partners when appropriate.

All applicants are strongly encouraged to contact program staff because it may be particularly challenging to prepare competitive grant proposals in cancer CAM research.

Program staff may assist investigators in several ways including:

- assisting applicants in locating funding opportunities;
- directing applicants to grant mechanisms that match the goal or intent of the project and experience of the investigator and find the “best fit”);
- discussing the science and research relevant to the program director’s program;
- providing technical assistance to the applicant;
- describing the program’s priorities and areas of increased interest;
- helping applicants network and identify areas of needed expertise;
- assisting in identifying appropriate review committees and potential ad hoc reviewers; and
- accepting proposals with budgets greater than \$500,000 (applicants must contact and have Program Director approval to submit such projects).

Program Directors serve as a source of information, support and guidance throughout the grant development, review, award and administrative process.

Grant Development: Challenges in Developing Proposals in Cancer CAM

Grant Application Development:

Grant applications should contain these sections: Abstract, Introduction, Specific Aims, Significance (literature review and background), Research Plans (methodology), Budget, and Biographical Sketch.

Applicants should be familiar with the required sections of the grant application. Challenges in developing research proposals are not always unique to cancer CAM. The Cultural and Qualitative Research Special Interest Group at the NIH developed a document which describes the required Research Sections. Relevant sections have been adapted here for cancer CAM research (for the complete document, see Qualitative Methods in Health Research: Opportunities and Considerations in Application and Review, <http://obssr.od.nih/Publications/Qualitative.PDF>).

Detailed descriptions of these sections as well as specific issues related to cancer CAM research are described in the following.

Specific Aims

The specific aims are the questions, hypotheses, or overall theories that the research is seeking to address or test. The applicant should describe the long-term goal or ultimate purpose as well as the specific aims to be accomplished during the proposed research.

Cancer CAM research may address broad and complex questions that are not always fully articulated. The applicant expects that key insights may emerge during the course of the research that will steer the project in future directions. It is necessary to strike a balance between reasonably achievable aims and openness to unanticipated findings. As the term “specific aims” implies, reviewers expect clearly delineated, precise research goals. Failure to move beyond broadly phrased, general statements in this section to specific goals weakens the argument that the study will produce important findings.

It is generally best to state a limited number of clearly focused aims. The applicant should carefully consider whether to frame the aims as hypotheses or as questions. A succinct description stressing the innovative nature of the study will help to engage the reader and underscore the project’s significance. The researcher should take care not to overstate the anticipated outcomes or appear overly confident of the intended effects. This is especially problematic in CAM intervention proposals. While investigators may show confidence in a particular intervention, the application should maintain a neutral tone and reflect the investigator’s objectivity to avoid concerns of “true believer” biases. The aims should be feasible for the given time, methods, and stated goal. A clearly and precisely worded statement about the examination of under-studied issues or uncertain relationships that appears to be achievable within the timeframe and resources available is recommended.

Once the specific aims are formulated the applicant should articulate exactly how these aims relate to each of the remaining application sections. For example, specific aims should be strongly linked to the research methods and the analytical processes. Be sure to edit to insure that the statements and restatements of the goal and aims are consistent throughout the various sections.

Background and Significance

This section briefly sketches the background leading to the present application, critically evaluates existing knowledge, and specifically identifies the knowledge gaps which the project is intended to fill. It also concisely states the importance and health relevance of the research described in the application by relating the specific aims to the broad, long-term objectives.

Here, the applicant has the opportunity to display knowledge of the field, ability to critically analyze the extant research, and to show how the proposed work will extend a research area, fill a gap, and, most importantly address public health. The background and significance section provides a well-reasoned and compelling argument for the importance of the research aims described in the “Specific Aims” section and for the appropriateness of the methodological approach proposed in the “Research Design and Methods” section.

The literature review should focus on research that is highly relevant to the planned study in such as way as to communicate gaps in existing understanding, to suggest the importance of the

planned study to address these gaps, and to expand the frontiers of scientific knowledge. Reviewers expect a thoughtful, balanced, and critical evaluation of the research literature not just a summary of what has been reported in other studies. The literature review should also provide the basis for the choice of concepts being investigated, the conceptual framework underlying the research, and the methodological approach proposed. In cancer CAM research, it may be challenging to find substantial supportive preliminary data. When possible, applicants should provide evidence that the CAM approaches have worked well for studies that have similar characteristics to the planned study. An applicant may wish to provide specific examples of how results of their previous similar research have made a significant contribution.

A commonly identified weakness in applications is that applicants spend too much effort citing too broad a range of material that has been written on the general topic and not enough effort on organizing the review in light of the specific area they want to investigate. On the other hand, reviewers will be looking to see that the review is complete and that all important studies or areas are included. Applicants should be careful to include the appropriate and relevant range of research studies. Care should be taken to write with a balanced tone while identifying and conveying the strengths and the weaknesses of existing studies. Finally, although the “Background and Significance” section should be substantive and demonstrate insight, breadth, and mastery, the applicant is advised to stay within the recommended page-limit guidelines.

The applicant should state the background to the issue or topic of study (that is, its general and broadest implications and relevance to various public constituencies) and the significance of the study aims to particular public health issues, concepts, data, and/or current practices, as appropriate. Applicants should keep in mind that “Significance” is one of the five review criteria by which the application will be evaluated (see Research Project Evaluation Criteria, page 22) and should consider the following questions in conceptualizing and describing the project: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field? Supportive evidence for the significance is provided through the literature review.

Preliminary Studies

This section should provide an account of the principal investigator’s preliminary studies pertinent to the application and/or any other information that will help to establish the experience and competence of the investigator to pursue the proposed project.

The preliminary studies should provide the basis for the argument to conduct the study in the manner proposed. In this section, the applicant has the opportunity to demonstrate competence with the methods and issues of concern to the proposed study, and to describe related work and data that led to the proposal. This section can document the applicant’s competencies at concept development, data collection and modes of analyses, and successful project completion and publication. Provide brief but detailed statements about prior studies, including aims, size of study group, design, kinds of data, analytic techniques, and key findings. Be sure to identify strengths and weaknesses. Describe how prior work contributed to the proposed design and methods. Reasoning through the limitations of previous work is useful, especially if the applicant can propose substantial improvement and expansion.

This section provides a forum to show precisely how the applicant's past cancer research (both conventional and related to CAM) has led to useful findings and supports the ability to undertake the proposed research. Establishing the applicant's record of publications pertaining to the specific population or methodology is essential. If necessary, amplify features about the investigators not stated in the biographical sketch.

In many areas of cancer CAM, writing about preliminary studies can present a challenge. If this is the situation, the applicant should showcase the staff's specific experience and expertise that makes them uniquely suited to conduct the proposed research. If they have used similar methods and techniques in a different substantive area, a short description of such studies, focusing on the methodological similarities, would be appropriate. Some pilot work could strengthen the application. A preliminary analysis of even a small amount of data allows the applicant to demonstrate the feasibility of the proposed data collection and analysis process.

Research Design and Methods

The Research Design and Methods section of the PHS 398 application for grant support (page 16) instructs applicants to:

Describe the research design and 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 the achieve the aims. As a 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.

Each of the components comprising this section of the research plan are discussed below. There are certain features of a good application that apply equally across all components. Two critical characteristics of a good design section are consistency in language and concepts throughout and integration of aims and questions through all parts of the plan. In addition, discussion of the strengths and limitations of the methods that will be used as compared to alternatives not selected is a useful aspect of the justification for the overall research plan. Another characteristic is a well-balanced, critical analysis of the information the study can and cannot provide.

The research questions or overall theory that will be addressed were described in the specific aims, and the background and significance sections of the research plan. The research design and methods section describes how the specific aims will be accomplished. The key consideration in laying out this section of the application is whether the proposed research design, sampling strategy, data-collection methods and procedures, and data analysis and interpretation approaches are the most appropriate, all things considered, for accomplishing the specific aims of the study. A plan that is well-thought-out, scientifically logical, and flows smoothly is one part of the proposal. In addition to sound scientific rationale, a good proposal also provides sufficient descriptive detail for each step and a timeline for the overall process.

Each element of the research plan, for example, the conceptual/theoretical framework guiding the study, sampling methods and sample characteristics, the data-collection approaches and procedures, and the analysis and interpretation of the data, is equally important in the overall plan for how the study will be conducted. The discussion of each research design element can be organized and presented in a way that conveys the linkage between the specific aims of the study and all other elements of the research plan and emphasizes the logical flow and integration of the research plan.

Design

The first part of this section describes the type of research design used. A brief introductory statement of the overall research strategy and the defining features of the design provides an overview of how the research will actually be conducted and may offer a restatement of the links between the theoretical and methodological perspectives reflected in the study. A brief overview could convey for example, whether the aims of the study are descriptive, hypothesis testing, or some combination; whether one approach, or an integrated approach will be used; whether data will be collected at one or multiple points in time; and how the population is defined. The chosen design is reflected in the specific aims and its influence over ensuing plan components is noted in each section.

There are several challenging issues in the research design of cancer CAM trials. In recognition of these issues, the NCI's Office of Cancer Complementary and Alternative Medicine established a series of expert panels to assess and critique the state of the science in research methodologies in cancer CAM research. Panelists from both conventional and CAM research apply their knowledge and expertise to specific topic areas within cancer CAM. Panelists identify the major methodological challenges in cancer CAM research and propose potential solutions. This process serves to assist grant applicants by illustrating the types of issues that should be addressed in cancer CAM research proposals. See Figure 3 for a summary table of strategies proposed by the first expert panel (*Expert Panels in Cancer CAM Research: Developing the State of the Science in Research Methodologies. Expert Opinions on Methodology: Development of Cancer CAM Symptom Research*, Bethesda, Maryland, 2001. Copies of this document are available through the NCI's Office of Cancer Complementary and Alternative Medicine at ncioccam-r@mail.nih.gov). In addition to the issues raised by this panel on symptom research there are other methodological concerns relevant to a variety of types of cancer CAM research.

Placebo/Controls

One of the most challenging issues applicants face in developing cancer CAM research designs involves the development of appropriate controls, shams, and placebo interventions. The creation of truly inert controls that will not cause independent beneficial or harmful effects in a research trial is of fundamental importance in the design of rigorous CAM research.

In developing placebo controls in botanical or dietary supplements, it is preferable to use placebo substances with same taste, smell, and size. In developing controls for CAM intervention trials, it may strengthen a proposal to include control groups that are designed to control for specific confounding variables. It is helpful to identify potential confounding variables and explain how a particular control group was selected and which confounds it is designed to address. Make sure

the control/group fits the stage of the project. If a feasibility study is proposed, control groups are not needed. The rationale for inclusion of control groups, details about the kinds of groups and what variables they are designed to address, should be clearly discussed in the proposal. If a feasibility study is proposed, the design should include endpoints that make sense for a feasibility study. If a pilot study is proposed, appropriate control groups and endpoints should be included that make sense for pilot studies.

Standardized vs. Individualized approaches

There has been an ongoing debate among clinicians and researchers alike regarding the most appropriate approach to study certain CAM interventions. Some investigators propose that to study an intervention, it is most appropriate to study it in the manner in which it is practiced, which often means providing interventions that are tailored to the individual. Researchers may balk at this approach, concerned that individualizing an intervention precludes its scientific study—an intervention needs to be standardized across subjects in order to draw meaningful conclusions. Proponents of individualized approaches counter with the concern that once an intervention is standardized, its efficacy may be compromised, and the research no longer utilizes the most potent and clinically useful form of the intervention. This is a complex methodological issue which crosses all areas of CAM research, but is more problematic for therapeutic interventions drawn from alternative systems of medicine (i.e. Traditional Oriental Medicine, Auyervetic) as well as for behavioral or mind-body approaches to symptom management.

There are two major study design issues to consider in CAM intervention research: an individualized approach or a standardized intervention. The controversy concerns achieving a balance between conducting a trial of a single intervention that does not accurately reflect true clinical practice or designing a multifaceted intervention trial that is complicated to design and implement and may not reflect the actual practice of the CAM intervention.

In proposing clinical research with a CAM intervention, the Research Design section should include a rationale for choosing the type of approach. Both approaches have advantages and disadvantages. The critical issue for applicants is to include a compelling rationale for the design approach selected. The proposal should demonstrate that the applicant is aware of these issues and is thinking carefully about them in developing the research design.

Study Design: Phase ?

Clearly define if a clinical research proposal is for a Phase I, II or III trial. Whatever phase trial is proposed, applicants should include a compelling rationale for its use for this intervention in this study population. Researchers often propose moving directly to a Phase III clinical trial with CAM products and interventions based upon the history of their use in alternative medical systems. While its history may help support its use in research, it is not necessarily sufficient to justify moving directly to Phase III trials. Prior experience may not have been with the same population (e.g. cancer patients) or may not have been used in combination with current cancer treatment regimens.

Strategies for Applicants in Cancer CAM Symptom Research

Placebo/Shams/Control Groups:

- Use placebo to demonstrate whether a therapeutic intervention has effect.
- Use active comparison to demonstrate how strong an effect an intervention may have.
- Create placebos and shams as similar as possible to intervention.
- Defend strategy of including or not including comparison groups.

Individualized or Standardized Approach to CAM Interventions:

- Discuss advantages and disadvantages of each approach.
- Provide compelling rationale for choice.
- Consider integrating individualized approach within standardized format.

Measurement Issues:

- Include hypotheses/rationale about why intervention would affect these symptoms.
- Use standardized tools that have demonstrated validity and reliability.
- Use tools that measure most common and most distressing symptoms.
- Consider tools that measure multiple symptoms.
- Consider and address patient burden.

Selecting Phase:

- Defend proposing Phase III without Phase I or Phase II data—does “thousands of years use” suffice?
- Address dosing issues—if don’t know dosage information, get preliminary data
- Give enough detail for replication

Investigational New Drug (IND) Issues:

- May require IND even if available over the counter—depends upon use.
- For NIH proposals, INDs may not be required—contact FDA and NIH program staff to inquire.
- Phase I/II studies may not require preclinical data: Phase III may require more toxicity data.
- INDs encouraged as the process can improve study design and increase likelihood of usable data.

Ethics:

- Demonstrate value of CAM research as a legitimate adjunct to conventional medical research.
- Disclosure of conflict of interest to patients is essential.
- Describe how vulnerable patients are recruited and enrolled to clarify and ensure informed consent.

Statistical Issues:

- Define primary and secondary endpoints.
- Choose measurement tools that focus on those endpoints.
- Include appropriate power analysis.
- Use stratification to account for confounds.
- Detail how to address patient attrition and/or missing data.
- Discuss both statistical significance and clinical significance.

Figure 3. Strategies for Applicants in Cancer CAM Symptom Research

Additional Methodological Issues in Cancer CAM Research

Multidisciplinary Approaches in Cancer Treatment

Often investigators are interested in investigating multidisciplinary approaches in cancer care. The advantages of studying the entire approach versus a step-by-step method of isolating and adding approaches should be discussed, and a compelling rationale defending the chosen approach should be included in the proposal.

Accrual and Selection Biases

Another important aspect of the research design is the specification of the criteria for determining who will, and will not, be included in the sample. For example, will only a certain age range, gender, or diagnostic group be included? Related to the selection criteria is the issue of the representativeness of the sample.

In addition, applicants need to be realistic in their estimates of accrual rates in clinical CAM research. Accrual in clinical investigations using CAM products and interventions may be particularly challenging in accrual especially if randomization of subjects is planned. Subjects may object to randomization to a non-intervention arm as these interventions are often available outside the experimental setting. Applicants should also address issues related to potential selection bias. Subjects who are willing to enroll in CAM research may or may not be representative of the proposed study population. Potential impact of this type of bias should be discussed in the application.

Extra-experimental Use of CAM

The applicants should address the issue of concomitant use of CAM experimental products or interventions. In traditional cancer research, investigators do not have to be concerned that subjects in the control group will take the active experimental drug or treatment because they simply cannot get access to it outside of the trial. In CAM research, subjects often can easily buy the same or a similar product as that under study or visit a practitioner who can administer an intervention (e.g. acupuncture). Investigators need to include discussion of this issue and appropriate steps taken to address this concern.

Study Population

The issues of acculturation and language may raise methodological (for example, access, consent, recruitment and retention) as well as scientific (for example, instrument validity and translation) problems to be addressed in research on ethnic populations. There are also special issues involved in sampling for hidden populations (for example, access) that may require specific strategies. Applications should include a discussion of these potential challenges.

Description of CAM Product or Intervention

Applicants interested in investigations that involve complex natural products (e.g., botanical extracts) need to provide enough detailed information in their proposals for NCI staff and review committees to evaluate whether these products are of sufficient quality for research. Applicants need to describe how the quality of the products will be insured. Information about supplier, lot, and potential containments should be included. If applicants plan to study a complex mixture, rationale for the use of that mixture should also be included. A discussion of the advantages and disadvantages of using mixtures (isolation versus potential synergy) is often helpful. The levels

of characterization, standardization, stability, purity, and optimization of the presumed active ingredient or ingredients may vary. Natural products should be chemically characterized as thoroughly as possible, using the most appropriate state-of-the-science method for this process. Some investigators using proprietary mixtures struggle with how much detail about the mixture to include in a proposal. Applicants should provide enough detail for appropriate scientific review.

For CAM interventions with practitioners, specific issues are often raised in review. Often there are no standards of practice for many of these interventions. It is important to demonstrate reliability and consistency of the practitioners of these interventions. Applicants should discuss in detail rationale for using one practitioner or for using several. When using several, detailed information about how practitioners will be chosen, trained to participate in the research, monitored and evaluated for reliability is important to include in the proposal.

Data Collection, Analyses, and Interpretation:

This section of the application addresses data collection instruments, methods, and procedures. It should include complete explanations of each of these areas and how the methods used will address the research questions.

Data collection strategies should be specific, in as much detail as possible, and include procedures for monitoring the quality of the data, including, for example, how data collectors will be trained and supervised and how information will be cross checked and triangulated with information from other data sources. Elements of quality monitoring of the data collection process might also include periodic checking of the intervention for reliability and consistency. Some researchers videotape practitioners to assess quality control.

Measurement Issues

Among the most important issues in the development of a clinical research design in cancer CAM is the appropriate selection of measurement tools. If available, applicants should use standardized tools that have demonstrated validity and reliability in the current study population. Care should be taken to define primary and secondary endpoints and choose the measurement tools that focus on those endpoints. In addition, applicants should strive to use the fewest number of instruments possible to assess the most compelling information.

In addition, consideration of patient burden, that is people's tolerance and stamina for completing measurement tools (both an issue of data quality and of human subjects protections) is an important issue. Applications that include non-English speakers will want to address the language of the interviews, translation procedures, and the use of translators.

Once again, a clear explanation of how each instrument or data collection method relates to and answers a specific aim is useful in demonstrating continuing integration and consistency in the plan.

Data Analysis

The data analysis strategy lays out the specific procedures for addressing each of the research questions and/or hypotheses, and the nature and form of the expected results.

Pilot data can be helpful in constructing a preliminary or hypothetical coding scheme. Similarly, tables can be used to demonstrate the hypothetical kinds of data that will be obtained and how they will be analyzed.

Data Interpretation

While there is no heading for data interpretation in the application kit, it is useful to describe the process for how the investigator will arrive at data integration and conclusions. The potential significance of the findings for both the immediate questions and broader issues can be addressed here. The process and procedures for integration and interpretation of data from various sources is particularly important when using more than one data source.

Budget

All general principles of developing and describing a research budget apply to cancer CAM research as they would to any research methodology. Significant budgeting problems faced in cancer CAM research include the added cost of collaborating with expert CAM practitioners for clinical intervention protocols, the costs associated with obtaining a quality controlled product and developing appropriate placebos for botanical products and dietary supplement studies. Applicants encounter problems in review when the budget does not adequately reflect these needs. Applicants frequently make the mistake of underestimating their budgets. The budget and timeline must reflect the effort needed to conduct a good data analysis. When reviewers are faced with an unrealistically low budget or short timeline for a project, they may interpret this as lack of experience or judgment on the part of the researcher and view the application negatively.

In December of 1998, NIH announced the use of modular budgets for certain grant applications. Applications whose total direct costs do not exceed \$250,000 per year are eligible to be submitted as modular grant applications. For the purpose of streamlining applications and budget development, modular budgets are submitted in modules of \$25,000.00 rather than being broken down into greater detail. If the applicant thinks there may be anything at all unusual or inordinately expensive about a proposed budget, he or she would be wise to include such a detailed justification as an appendix. Full information on NIH modular grants is available at <http://grants.nih.gov/grants/funding/modular/modular.htm>. Any questions about this are appropriately directed to the applicant's program official.

Additional Application Requirements:

All applications must contain sections that address the following: Human Subjects, Inclusion of Certain Populations, and Data Safety Monitoring. Failure to include any of these sections results in the application being returned to the investigator without review. It is important to read all requirements carefully. In addition, applicants who are proposing clinical research projects with botanical and dietary supplement products should investigate the need for an Investigational New Drug application.

Human Subjects:

Since this is an area subject to constant change, one area in which applicant error can have dire consequences, it is best to begin with the official sources. All participants in the NIH application process are encouraged to be thoroughly familiar with the latest federal research regulations. The Office for Protection from Research Risks (OPRR) has moved from the NIH into the Office of

the DHHS Secretary and has been renamed the Office for Human Research Protections (OHRP) with a web site at <http://ohrp.osophs.dhhs.gov>. The guidelines span the different levels of research involvement and discuss numerous special topics. Readers of this document may find the Belmont Report, which annotated the principles that apply across all types of research, of particular interest. There is also a web site for the NIH Human Subjects Committee (<http://odoerdb2.od.nih.gov/oer/committees/hsp/hsp.htm>) which is composed of subcommittees that address specific items within the other guideline document. For additional information regarding Human Subject Terms, see Appendix III.

There are also revised guidelines for the inclusion of various populations in research designs. The modified policy can be found at <http://ohrp.osophs.dhhs.gov/index.htm> and reflects revision to the relevant standard language for RFAs, PAs, and RFPs and awards. These modifications require that applications, or protocols provide a description of plans to conduct analyses to address differences by sex/gender and/or racial/ethnic groups and that all investigators are to report accrual, and conduct and report analyses by sex/gender and/or racial/ethnic group differences. The results of the analyses must also be reported to NIH in Progress Reports, Competitive Renewal Applications (or Contract Renewals/Extensions) and in the Final Progress Report.

In addition, for the purposes of generalizing research results and increasing the range of individuals who benefit from research, NIH is mandating the inclusion of women, children, and diverse ethnic groups in its funded applications. Applicants can check for the latest regulations at a new web site for Inclusion of Women and Minorities which can be found at http://grants.nih.gov/grants/funding/women_min/women_min.htm and contains the relevant documents.

Overall, competitive applications involving human subjects must demonstrate an awareness of the most current ethical guidelines and address all of the possible ethical concerns of the planned study. Applicants should show that they have thought of the worse-case scenario, have taken proactive measures to prevent it, and have remedies in place to deal with it. Applications involving special populations, such as children or cognitively compromised individuals, must demonstrate the researcher's ability to ethically and effectively work with the target population. Regardless of the particular human subject issues involved in the proposal, applicants can do much of the work on this section long before proposal submission.

It is important to note that while investigators must include a discussion of these topics in their proposals, investigators do not necessarily have to include all groups in their research. There are occasionally scientifically acceptable reasons for study populations to be limited (e.g., women are not required to be included in clinical investigations of prostate cancer). It is not sufficient, however, to have limited representation in a study population due to difficulty or expense in accrual of these populations.

Data Safety Monitoring

If a clinical research trial is proposed, the applicant must specify plans for monitoring to insure the safety of participants. The type of monitoring depends on the size and complexity of the trial and on the degree of risk to participants.

Phase I and Phase II studies require a Data and Safety Monitoring Plan (DSMP), which may be administered by the investigator, by a project manager, by a member of the NCI program staff, or by an individual designated by the investigator or NCI staff. Or, some combination of these individuals may work together to administer the plan.

A Data and Safety Monitoring Board (DSMB) is required for all Phase III clinical trials. Phase III trials are tests of interventions which, if found to be successful, would likely influence clinical- or public-health practice.

For more information about the topics to be included in the discussion of data and safety monitoring, see the NCI Data and Safety Monitoring Guidelines: Summary in Appendix IV.

Investigational New Drug (IND) Applications:

Current federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, he/she must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

Please review the FDA website for further information:

http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

Common Issues in Cancer CAM Applications: Suggestions for Applicants

NCI's Office of Cancer Complementary and Alternative Medicine program staff has identified some of the most common problems and weaknesses in cancer CAM grant proposals to the NCI. Specific suggestions to applicants are provided below.

Tips for preparation:

Contact program directors. Program directors are available for technical assistance as their schedules allow. Applicants are encouraged to submit concepts/abstracts of their projects to the program director so he or she may guide the applicant to the most appropriate grant mechanism and provide technical assistance when appropriate.

Confirm appropriate mechanism. Applications need to be prepared with the review criteria in mind. Confirm budget limitations, page limitations and other requirements. Read and re-read announcements very carefully. Confirm receipt dates.

Include essential sections and information. Include Human Subjects, Inclusion of Gender, Minorities and Children in research, and address Data Safety Monitoring. In the near future, applicants will also be instructed to address Data Sharing (for more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>).

Use state-of-the-science methodological designs appropriate for the cancer topic (e.g., appropriate immunology assays) as well as for the CAM component. NCI expects the highest quality science regardless of the CAM nature of these projects.

Create the appropriate research team. Get the highest level of expertise and include letters confirming participation in the application. Make sure these consultants and co-investigators participate in the development of the proposal.

Include experienced co-investigators and consultants on the research team to strengthen the proposal. By enlisting a consultant, you show the reviewers that you are aware of your scientific limitations and know where to find the appropriate expertise. Have the consultants participate in preparing the application.

Demonstrate in writing the proposal that you know what you are doing. Convince the reviewers and NCI that you are also aware of limitations and that you have the appropriate expertise to guide you. Identify the review committee, if possible. IRGs are listed on the Center for Scientific Review (CSR) website at <http://www.csr.nih.gov/studysec.htm>. Special Emphasis Panels (SEPs) are created as needed, but whenever possible, applicants should familiarize themselves with the range of expertise on review committees and write the grant proposal with this audience in mind.

Tie the proposal to the research priorities of the NCI. Review the most recent NCI Budget Document for identified areas of interest (The National Cancer Institute, The Nation's Investment in Cancer Research, A Budget Proposal for Fiscal Year 2003. Copies can be ordered by fax at 301-330-7968, by email at sisocc@nih.gov or by telephone at 1-800-4-CANCER. These documents may also be viewed online at <http://www.nci.nih.gov>).

Investigate the necessity for filing an IND application with the Federal Drug Administration (FDA). Contact FDA or NCI program staff for information or appropriate referral for information. Just because a natural product or dietary supplement is available “over the counter” does not necessarily mean that a product is exempt from IND regulations in a research proposal.

Inclusion criteria for the presence of the dependent variable in the study population should be included. This is especially an issue for research in cancer symptom management. It is essential to document that the study population experiences whatever is the focus of the study.

Write the proposal for the appropriate funding mechanism and remind the reviewers of this mechanism. If the proposal describes a developmental project, remind the reviewers, who are more frequently reviewing R01 studies, by using that language in the text. Include information on where this project will go next. Suggesting a “larger trial” will follow is typically not sufficient. Describe how this project fits into a research program, how it moves the science

forward, and how the developmental project answers specific issues that need to be addressed prior to a larger R01 investigation. Give the reviewers some sense of what the R01 will look like.

When preparing the application, it is important to clearly define the timeline. Past studies that have been performed and their timelines can be used to strengthen your proposal. Applicants should clearly state specific project activities at key points in the project timeline. These activities should coincide with your budget development.

Justify the requested funding and provide a comprehensive picture of the current state-of-the-science and what more is needed to support further research on your proposed topic.

Applications that reflect the input of expert statisticians are clearly evident to reviewers. Including a statistician in the development of a proposal strengthens its competitiveness.

Have a colleague that is unfamiliar with your topic read your application. This objective review will prevent you from making assumptions in your proposal that are not clearly stated. You know what you are planning to do, but this helps ensure that someone reading your application will also know what you are planning to do.

Don't leave anything open for interpretation. Be very clear and concise.

When developing a research proposal, carefully consider your choice of intervention and provide a compelling rationale for your choice. Include a discussion of the data and potential theories supporting your hypotheses. Also address the issues that may not support the research so you can effectively present the case for the value of the proposed research.

Carefully consider your study population. Your application should include a compelling rationale for the use of this intervention in this specific study population.

Applicants should address potential safety issues when CAM products and interventions are proposed for clinical research. Specific information should be included that addresses potential toxicities as well as concerns when using CAM in combination with conventional cancer therapies. The addition of CAM modalities in treatment should not compromise the safety and efficacy of conventional cancer therapy.

Submission

Cover Letters:

Approval from program staff is needed for applications requesting over \$500,000 in direct costs. NIH policy requires that any competing application (new, continuation, revised, supplement) requesting over \$500,000 in direct costs in any year must be accepted by an Institute or Center prior to assignment for review. For more information, visit (<http://grants.nih.gov/grants/guide/notice-files/not98-030.html>).

Upon receipt, each application is assigned to one Program Director. The Center for Scientific Review assigns the application to an Institute or Center and to a Initial Review Group (IRG) or Special Emphasis Panel (SEP). The Institute or Center's referral personnel will then assign the

application to the appropriate program. Applicants may request in a cover letter the assignment of the application to a particular Institute and/or IRG. These requests are taken into consideration by CSR. Applicants may also request secondary assignment of their application. This enables the applicant to be considered for funding by more than one Institute. The Program Director may help identify appropriate Institutes for secondary assignment. In the case of cancer CAM applications, several Institutes may be listed as secondary assignments as well. Program Directors may also assist in identifying appropriate review committees for cancer CAM applications.

Applicants who have received assistance in their grant preparation or who have contacted program staff for approvals prior to submissions (i.e. budget limitations) should also mention in their cover letter the program staff member by name and provide that person's contact information. When appropriate, applicants may include in their cover letter requests for specific review expertise. Especially in cancer CAM topics, it may be helpful for applicants to identify certain areas of expertise and request ad hoc reviewers if necessary.

Instructions for Submission:

Unless stated otherwise, applications must be sent to the Center for Scientific Review (CSR) and on the appropriate application form (usually the PHS398). (For additional information on this process and submission details, please refer to <http://grants.nih.gov/grants/funding/phs398/phs398.html>). It is important to refer to the CSR website for notification of changes in procedures or policies in grant submissions.

Applicants need to submit the materials in one package by the due date specified in the announcement or the regular receipt dates. If an applicant is responding to a specific announcement (RFA, PA, etc.), it is important to indicate the announcement on the face page of the application.

There may be additional instructions for submission of responses to Requests for Applications. Applicants submitting Investigator-Initiated Interactive Research Project Grant (IRPG) applications should include all of the applications and appendix material in one package with a cover letter identifying the applications as such.

Receipt, Assignment and Review

The Public Health Service receipt, review, and award schedule is provided in Appendix II. Applicants are strongly encouraged to confirm receipt dates with program staff.

Submit a complete application. Incomplete applications will be grounds for the application to be without peer review. An application will be returned if it is illegible, if the instructions were not followed, or if the material presented is insufficient to permit an adequate review.

Unless specifically required by these instructions (e.g., vertebrate animals certification), do not send supplementary or corrective material after the receipt date unless the Scientific Review Administrator (SRA) of the Scientific Review Group solicits or agrees to accept this information. The application must be complete and accurate at the time of submission because there is no guarantee that the peer reviewers will consider late material.

Submission of identical applications to different agencies within the PHS or to different Institutes within an agency is not allowed. Essentially identical applications will not be reviewed except for: 1) individuals submitting an application for an Independent Scientist Award (K02) proposing essentially identical research in an application for an individual research project; and 2) individuals submitting an individual research project identical to a subproject that is part of a program project or center grant application.

Application Assignment Information

As soon as possible after the receipt date, usually within six weeks, the CSR will send the principal investigator/program director and the applicant organization the application's assignment number; the name, address, and telephone number of the Scientific Review Administrator of the SRG to which the application has been assigned; and the assigned Institute contact and phone number.

All inquiries regarding the assignment, review, or recommendation on funding of applications are to be made only to NIH officials. It is inappropriate to contact consultants serving on advisory or review committees regarding these issues.

The Peer Review Process

Competing grant applications submitted to the NIH must be submitted through the Division of Receipt and Referral, CSR, NIH unless otherwise stated. Administrative information about the application is entered into a computer system. The application is then assigned to the appropriate SRG and Institute(s). Assignment is based on the scientific content of the application using established referral guidelines.

Most applications submitted to the CSR will be reviewed through a two-tier system. The first level of review will be performed by an SRG, often called a study section or review committee. The purpose of the SRG is to evaluate the scientific and technical merit of applications. The SRG does not make funding decisions.

SRG members will be instructed to evaluate research applications by addressing five review criteria (see below) and assigning a single, global score for each scored application. The score will reflect the overall impact that the proposed research could have on the field based on consideration of the following NIH research evaluation criteria. RFAs and other types of grants may have different and/or additional review criteria. It is important to carefully read the RFA or other announcement for any specific review criteria for that announcement.

Note: Applicants must never contact reviewers regarding their applications since discussion of the scientific content of an application or an attempt to influence review outcome will constitute a conflict of interest in the review. Reviewers are required to notify the SRA if they are contacted by an applicant. Communication by the applicant to a reviewer will result in the return of the application without peer review.

Research Project Evaluation Criteria

Significance

Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field? It is important when describing a CAM or CAM-related intervention to address its potential significance in terms of scientific knowledge or potential improvements in clinical practice beyond what may be available in conventional Western medical approaches. For example, reviewers may question whether studying acupuncture would be compelling if it is used for an outcome for which there is an inexpensive, safe and effective conventional treatment already in use.

Approach

Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

Innovation

Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies? In cancer CAM topics, novel concepts are not difficult to identify. However, presenting a compelling rationale for the use of the novel CAM approach to a specific research problem is important to include in grant proposals.

Investigator

Is the investigator appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)? In cancer CAM, it is often necessary to seek out consultants and, in clinical research, practitioners. Program staff can assist in identifying expertise and providing opportunities for networking. Applicants that have identified the strengths of investigators and sought out appropriate expertise by including appropriate consultants and practitioners are often more competitive in the review process.

Environment

Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

While these review criteria are intended for use primarily with unsolicited research project applications (e.g., R01, P01), to the extent reasonable, they will also form the basis for the review of solicited applications and non-research activities. Additional review criteria may be listed in specific announcements.

Human Subjects/Vertebrate Animals

In conducting peer review for scientific and technical merit, SRGs will also evaluate the involvement of human/animal subjects and proposed protections from research risk relating to

their participation in the proposed research plan according to the following four review criteria: (1) risk to subjects; (2) adequacy of protection against risks; (3) potential benefits of the proposed research to the subjects and others; and (4) importance of the knowledge to be gained.

When human subjects are involved in the proposed clinical research, the SRG will also evaluate the proposed plans for inclusion of minorities and members of both sexes/genders, as part of the scientific assessment of Approach criterion. The evaluation will be factored into the overall score for scientific and technical merit of the application.

Dual-Level Peer Review

As part of the initial merit review, all applicants will receive a written critique based on the comments and recommendations of the SRG. The review of most research applications will also include a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review.

The second level of review will usually be performed by the Advisory Council or Board of the potential awarding component (Institute, Center, or other unit). Council or Board recommendations are based not only on considerations of scientific merit, as judged by the SRGs, but also on the relevance of the proposed study to an Institute's programs and priorities. The review criteria can be found on the NIH Web site, <http://grants.nih.gov/grants/peer/peer.htm> or obtained from GrantsInfo, (301) 435-0714, Email: GrantsInfo@nih.gov.

Most common critiques for R21 applications in cancer CAM:

NCI's OCCAM program staff have attended as many review committee meetings of cancer CAM proposals as possible. Based upon this experience, the most common critiques from review committees of R21 cancer CAM grant proposals are presented below.

Too ambitious: The applicant is proposing too many Specific Aims to accomplish within the constraints of the funding mechanism.

Inadequate budget: The applicant has not included an appropriate budget for the proposed study. This critique is common when an applicant's Specific Aims are too numerous or complex for the constraints of the funding mechanism.

Needs additional expertise: The applicant failed to identify areas of weakness and develop an appropriate research team.

Weak statistics section: The application does not reflect the input of an experienced statistician. Often these applications lack an appropriate power analysis for the proposed design.

Unclear or poorly written: The proposal has spelling errors, or inconsistent details throughout application. This often results from applicants copying sections of their proposals from other documents and inserting them into the proposals.

Lack of detail: The application does not include enough information for reviewers to understand what is proposed and how it will be accomplished.

Lack of natural products characterization: The applicant has failed to include enough information about the chemical characterization of a natural product or adequate information about the source and quality of a product to be used in the research.

CAM intervention design issue: The applicant did not include a compelling rationale for the use of an individualized or standardized approach to CAM intervention or other methodological issues.

Conventional design issue: The proposal includes too many measures or too many variables to complete the study as proposed and/or to result in meaningful data.

Missing or inappropriate control group: Applicant did not include a compelling rationale for the placebo or control condition. This is an issue in preclinical as well as clinical research in cancer CAM.

After Review

Applications that are judged to be competitive (usually those in the top half of the scoring range), are assigned a priority score that ranges from 100 to 500 and, if reviewed by a CSR committee, given a percentile. The score represents a “raw” number; the percentile puts the score in the context of the overall voting pattern of that committee. Applications that are reviewed by Special Emphasis Panels are only given a priority score. All applicants are notified of their score (and percentile if appropriate) and are sent a summary statement of the critique and discussion of the review committee (sometimes called the “pink sheet”).

Feedback to applicants is very important. Once the principal investigator receives the summary statement, s/he may contact the appropriate Program Director (noted on the summary statement) for an interpretation of the reviews and the disposition of the application. In addition, program directors typically make every effort to attend review meetings in person and can assist investigators through the revision process as well.

It is important to note that there is a two-year and two-amendment limitation: the number of revisions of an application is limited to two, which must be submitted within two years of the original version of the application (see <http://grants.nih.gov/grants/guide/notice-files/not97-011.html>) Revised applications must include an Introduction that discusses the previous review and should mark the text to show where changes have been made. For more details on requirements related to application revisions see:

http://grants.nih.gov/grants/funding/phs398/section_1.html#intro_revised

SUMMARY

In summary, applications to NIH featuring cancer CAM must meet all general criteria required of any application. NIH instructions should be followed carefully. Program staff should be contacted for questions and assistance *during* application development. Do not wait until the time of submission. The applicant should consult program announcements and descriptions for guidance on content. The research plan described in the application must lay out a systematic plan of research and clearly specified data collection and analytic procedures. All sections of the plan should be clearly related to each other. The plan should flow directly from the specific aims, with direct discussion of how each aim will be achieved through particular data collection and specific analyses. It is highly recommended that this section be distributed to experienced reviewers (successful NIH grant writers) for comment and revision prior to grant submission. The section should be revised and re-written multiple times to remove all identifiable ambiguities and to be certain that all procedures are clearly and precisely laid out. Finally the entire product should present a coherent, clear and well-documented argument for the importance of conducting this particular research in the particular method specified.

APPENDIX I

Budget Mechanisms

<http://www3.cancer.gov/admin/gab/index.htm>

The NCI's budget is organized according to the following nine major funding areas:

- Research Project Grants.
- Cancer Centers and Specialized Programs of Research Excellence.
- Other Research Grants.
- Training.
- R&D Contracts.
- Intramural Research.
- Research Management and Support.
- Cancer Prevention and Control.
- Construction.

The following section, organized in the order outlined above, details each of the funding mechanisms used by the NCI.

Research Project Grants

Research Project Grants are awards for investigator-initiated research proposals. Several types of awards are made in this category, which vary in of the type of mechanism, type of applicant, total amount of support, and of length of time. Fiscal year 2001 research project grant expenditures totaled \$1,696,603,000 accounting for 45.2 percent of the NCI budget.

P01 Research Program Project Grant

Research Program Project Grants (P01s) support an integrated, multiproject research approach involving a number of independent investigators who share knowledge and common resources. A P01 has a defined central research focus involving several disciplines or several aspects of one discipline. Each individual project should contribute or be directly related to the common theme of the total research effort, thus forming a system of research activities and projects directed toward a well-defined research program goal.

R01 Research Project Grant

Research Project Grants (R01s) support a discrete, specified research project to be performed by the named investigator(s) in an area representing his/her specific interest and competencies. This is generally referred to as a traditional research project grant.

R03 Small Research Grant

Small Research Grants (R03s) provide research support specifically limited in time and amount for studies in categorical program areas. Small research grants provide flexibility for initiating studies that are generally for preliminary short-term projects. These grants are non-renewable.

R21 Exploratory/Developmental Grant

Exploratory/Development Grants (R21s) support the development of new research activities in categorical program areas. Support generally is restricted in level of support and in time.

R29 First Independent Research Support and Transition (FIRST) Award

FIRST Awards (R29s) provide a sufficient initial period of research support for newly independent biomedical investigators to develop their research capabilities and demonstrate the merit of their research ideas. This award mechanism is in the process of being phased out.

R33 Exploratory/Developmental Grant-Phase II

Phase II of the Exploratory/Development Grants (R33s) provide a second phase for the support for innovative, exploratory, and developmental research activities initiated under the R21 mechanism.

R35 Outstanding Investigator Grant (OIG)

OIGs (R35s) provide long-term support to encourage experienced investigators with an outstanding record of research productivity to embark on long term projects of unusual potential in a categorical program area. This award mechanism is in the process of being phased out.

R37 Method to Extend Research in Time (MERIT) Award

MERIT Awards (R37s) provide long-term grant support to investigators whose research competence and productivity are distinctly superior and who are highly likely to continue to perform in an outstanding manner. Investigators may not apply for a MERIT Award. After initial review, NCI staff and the National Cancer Advisory Board review competing R01 applications to select MERIT awardees. An initial five-year MERIT Award is followed by an opportunity for an extension of one to five more years, based on an expedited review of the accomplishments during the initial period.

R41 Small Business Technology Transfer (STTR) Grant—Phase I

Phase I STTR Grants (R41s) support cooperative research and development projects between small domestic for-profit organizations and research institutions. R41s are limited in time and amount and are used to establish the technical merit and feasibility of ideas that have a potential for commercialization. Generally, support for Phase I STTR awards may not exceed \$100,000 for direct and indirect costs and a fixed fee for a period normally not to exceed one year. Note: Phase I award levels and project periods are statutory guidelines. Therefore, applicants are encouraged to propose a budget and project that is appropriate for completion of the research project. Deviations from the guidelines must be well justified.

R42 Small Business Technology Transfer (STTR) Grant—Phase II

Phase II STTR Grants (R42s) support in-depth development of cooperative research and development projects between small domestic for-profit organizations and research institutions, limited in time and amount, for which feasibility has been established in Phase I (R41) and which have potential for commercialization. Generally, support for Phase II awards may not exceed \$500,000 for direct and indirect costs and a fixed fee for a period normally not to exceed two years. Note: Phase II award levels and project periods are statutory guidelines. Therefore, applicants are encouraged to propose a budget and project that is appropriate for completion of the research project. Deviations from the guidelines must be well justified.

R43 Small Business Innovation Research (SBIR) Grant—Phase I

Phase I SBIR Grants (R43s) support research efforts by for-profit domestic small businesses. The objective of this phase is to establish the technical merit and feasibility of proposed research or research and development (R&D) efforts and determine the quality of performance of the small business awardee organization prior to providing further Federal support in Phase II (R44). Generally, support for Phase I awards may not exceed \$100,000 for direct and indirect costs and a fixed fee for a period normally not to exceed six months. Note: Phase I award levels and project periods are statutory guidelines. Therefore, applicants are encouraged to propose a budget and project that is appropriate for completion of the research project. Deviations from the guidelines must be well justified.

R44 Small Business Innovation Research (SBIR) Grant—Phase II

Phase II SBIR Grants (R44s) continue those R&D efforts started in Phase I (R43). Awards will be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II application. Only Phase I awardees are eligible for Phase II. Generally, support for Phase II may not exceed \$750,000 for direct and indirect costs and a fixed fee for a period normally not to exceed two years. Note: Phase II award levels and project periods are statutory guidelines. Therefore, applicants are encouraged to propose a budget and project that is appropriate for completion of the research project. Deviations from the guidelines must be well justified.

R55 James A. Shannon Director's Award

Shannon Awards (RS5s) provide a limited award to investigators to further develop, test, and refine research techniques; perform secondary analysis of available data sets; test the feasibility of innovative and creative approaches; and conduct other discrete projects that can demonstrate their research capabilities and lend additional weight to their already meritorious applications.

U01 Research Project Cooperative Agreement

Cooperative Agreements (U01s) support discrete, specified, circumscribed projects to be performed by the named investigator(s) in an area representing their specific interest and competencies. This mechanism is utilized when substantial programmatic involvement is anticipated between the NCI and the recipient during performance of the contemplated activity.

U19 Research Program Cooperative Agreement

Research Program Cooperative Agreements (U19s) support research programs that have multiple projects directed toward a specific major objective, basic theme, or program goal, requiring a broadly based multidisciplinary and often long-term approach. Substantial Federal programmatic staff involvement is intended to assist investigators during performance of research activities, as defined in the terms and conditions of award. This mechanism can provide support for certain basic shared resources, including clinical components, which facilitate the total research effort.

U43 Small Business Innovation Research (SBIR) Cooperative Agreement—Phase I (see R43)

Phase I SBIR Cooperative Agreements (U43s) support projects, limited in time and amount, to establish the technical merit and feasibility of research and development (R&D) ideas that may

ultimately lead to commercial products or services. This mechanism is utilized when an assistance relationship will exist between the NCI and a recipient and in which substantial programmatic involvement is anticipated between the NCI and the recipient during performance of the contemplated activity. Cooperative agreement applications will be considered only for the topics specifically listed in the current SBIR Omnibus Solicitation. Note: Phase I award levels and project periods are statutory guidelines. Therefore, applicants are encouraged to propose a budget and project that is appropriate for completion of the research project. Deviations from the guidelines must be well justified.

U44 Small Business Innovation Research (SBIR) Cooperative Agreement—Phase II (see U43 and R44)

Phase II SBIR Cooperative Agreements (044s) support in-depth development of R&D ideas for which feasibility has been established in Phase I (U43) and that are likely to result in commercial products or services. Note: Phase II award levels and project periods are statutory guidelines. Therefore, applicants are encouraged to propose a budget that is appropriate for completion of the research project. Deviations from the guidelines must be well justified.

Cancer Centers and Specialized Programs of Research Excellence

The Cancer Research Centers Program as a whole contains a great diversity of research approaches to the problem of cancer, incorporating all applicable disciplines. Fiscal year 2001 Cancer Research Centers Program expenditures totaled \$279,731,000, accounting for 7.5 percent of the NCI budget.

P20 Planning Grant

Planning Grants (P20s) support planning for new programs, expansion or modification of existing resources, and feasibility studies for new approaches. Such awards have been particularly useful in the development of cancer centers and SPORES.

P30 Cancer Center Support Grant

Cancer Center Support Grants (P30s) provide support primarily for the research infrastructure of an active and unified cancer center for the purpose of consolidating and focusing cancer-related activities, increasing research productivity, promoting shared use of research resources and improved quality control, stimulating and promoting interdisciplinary and collaborative research, and increasing the rate at which research discoveries are translated into medical benefits.

P50 Specialized Center Grant

Specialized Center Grants (P50s) support any part of the full range of research and development from very basic to clinical activities and may involve ancillary supportive activities such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multi-disciplinary attack on cancer. These grants differ from Program Project Grants in that they are usually developed in response to an announcement of the programmatic needs of the NCI and later receive continuous attention from its staff. Centers may also serve as regional or national resources for special research purposes.

U54 Specialized Center—Cooperative Agreement

Specialized Center Cooperative Agreements (U54s) support any part of the full range of research and development from very basic to clinical; may involve ancillary supportive activities such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multidisciplinary attack on a specific disease entity or biomedical problem area. These differ from program project in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently receive continuous attention from its staff. Centers may also serve as regional or national resources for special research purposes, with funding component staff helping to identify appropriate priority needs. At the NCI, U54s support comprehensive partnerships between Minority Serving Institutions (MSIs) and the NCI-designated Cancer Centers for the benefit of both. These partnerships focus on cancer research and one or more target areas in cancer research training or cancer research career development at the MSI. These partnerships may also focus on cancer research and target areas in cancer education for or cancer outreach to minority communities.

Other Research Grants

Other grants include the Research Career Program and all other research grants not included in Research Project Grants, Research Centers, and/or Cancer Prevention and Control except for National Research Service Awards. The NCI Research Career Program includes all "K" awards. Fiscal year 2001 other research expenditures totaled \$269,201,000, accounting for 7.2 percent of the NCI budget.

K01 Mentored Research Scientist Development Award

Mentored Research Scientist Development Awards (K01s) provide research scientists with an additional period of sponsored research experience as a way to gain expertise in a research area new to the applicant or in an area that would demonstrably enhance the applicant's scientific career. NCI supports two K01 awards: the Howard Temin Award and the Mentored Career Development Award.

K05 Senior Scientist Award

Senior Scientist Awards (K05s) support outstanding established scientists who have demonstrated a sustained, high level of productivity, research accomplishments and contributions to cancer prevention, control and population sciences research. These awards provide protected time to devote to research and to act as mentors for young investigators.

K07 Academic Career Award

Academic Career Awards (K07s) support more junior candidates who are interested in developing academic and research expertise in a specific area or to support more senior individuals with acknowledged scientific expertise and leadership skills who are interested in improving the curricula and enhancing the research capability within an academic institution.

K08 Mentored Clinical Scientist Development Award

Mentored Clinical Scientist Development Awards (K08s) support the development of outstanding clinical research scientists. These awards provide specialized study for clinically trained professionals who are committed to a career in research and have the potential to develop

into independent investigators. NCI provides support for the K08 through the Clinical Investigator Award and the Minorities in Clinical Oncology Award.

K12 Mentored Clinical Scientist Development Program Award

Mentored Clinical Scientist Development Program Awards (K12s) support newly trained clinicians appointed by an institution for development of independent research skills and experience in a fundamental science within the framework of an interdisciplinary research and development program.

K22 Career Transition Award

Transition Awards (K22s) support newly trained basic or clinical investigators to develop their independent research skills through a two-phase program – an initial period involving an intramural appointment at NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the investigator in order to sustain or promote a successful research career. The NCI supports two K22 awards: the Scholars Program and the Transition Development Award. The NCI Scholars Program provides an opportunity for new investigators to begin independent research careers first intramurally within the special environment of the NCI and then to continue their careers extramurally at an institution of their choice. The NCI Transition Career Development Award is a fully portable mechanism that facilitates the transition of talented clinician cancer scientists, clinicians in patient-oriented cancer research and researchers in cancer prevention, control and the population sciences from the mentored stage of their careers to junior faculty or equivalent.

K23 Mentored Patient-Oriented Research Career Development Award

Mentored Patient-Oriented Research Career Development Awards (K23s) provide support for the career development of investigators who focus their research endeavors on patient-oriented research. The mechanism provides support for a period of supervised study and research for clinically trained professionals who have the potential to develop into productive clinical investigators

K24 Mid-Career Investigator in Patient-Oriented Research Award

Mid-Career Investigator in Patient-Oriented Research Awards (K24s) provide clinicians the opportunity to dedicate time for patient-oriented research and to mentor other clinical investigators.

K25 Mentored Quantitative Research Career Development Award

Mentored Quantitative Research Career Development Awards (K25s) support the career development of investigators with quantitative scientific and engineering backgrounds outside of biology or medicine who have made a commitment to focus their research endeavors on behavioral and biomedical research (basic or clinical).

K30 Institutional Curriculum Award

Institutional Curriculum Awards (K30s) support the development, conduct, and evaluation of the curriculum designed to improve the quality of the training available to aspiring clinical investigators.

R13 Conference Grant

Conference Grants (R13s) support national or international meetings, conferences, and workshops that are of value in promoting the goals of the National Cancer Program.

R15 Academic Research Enhancement Award (AREA)

AREA Grants (R15s) support small scale research projects conducted by faculty in primarily baccalaureate degree-granting domestic institutions. Awards are for up to \$75,000 in direct costs (plus applicable indirect costs) for periods not to exceed 36 months.

R24 Resource-Related Research Project

Resource-Related Research Projects (R24s) support research projects that will enhance the capability of resources to serve biomedical research.

R25 Cancer Education Grant

Cancer Education Grants (R25s) support the development and implementation of programs related to education, information provision, training, technical assistance, coordination, or evaluation. The NCI supports two distinct Cancer Education programs: the Cancer Education and Career Development Program and the Cancer Education Grant Program (CEGP). The NCI Cancer Education and Career Development Program (R25T) is an institutional grant program that supports the development and implementation of curriculum-dependent programs to train predoctoral and postdoctoral candidates in cancer research settings that are highly interdisciplinary and collaborative. The NCI Cancer Education Grant Program (CEGP) is a flexible, curriculum-driven program aimed at developing and sustaining innovative educational approaches that ultimately will reduce cancer incidence, mortality and morbidity, as well as on improving the quality of life of cancer patients. The CEGP awards (R25Es) address a need that is not fulfilled adequately by any other grant mechanism available at NIH. These awards are dedicated to areas of particular concern by the NCI.

S06 Minority Biomedical Research Support (MBRS)

Minority Biomedical Research Support (MBRS) grants provide funds to strengthen the biomedical research and research training capability of ethnic minority institutions, thus creating a more favorable milieu for increasing the involvement of minority faculty and students in biomedical research.

T09 Scientific Evaluation

Scientific Evaluation awards (T09s) provide the chairman of a training committee funds for operation of a review group.

U09 Scientific Review and Evaluation (Cooperative Agreement)

Scientific Review and Evaluation Cooperative Agreements (U09s) provide the chairman of an Initial Review Group (IRG) funds for operation of the IRG.

U10 Clinical Research Cooperative Agreement

Clinical Research Cooperative Agreements (U10s) support clinical evaluations of various methods of therapy and/or prevention in specific disease areas. These represent cooperative

programs between sponsoring institutions and participating principal investigators, and are usually conducted under established protocols.

U13 Conference Cooperative Agreement

Conference Cooperative Agreements (U13s) support international, national, or regional meetings, conferences, and workshops where substantial programmatic NCI staff involvement is planned to assist the recipients.

U24 Resource-Related Research Project Cooperative Agreement

Resource-Related Research Project Cooperative Agreements (U24s) support projects contributing to the improvement of the capability of resources to serve biomedical research.

U56 Exploratory Grant -Cooperative Agreement

Exploratory Grant Cooperative Agreements (U56s) support planning for new programs, expansion or modification of existing resources, and feasibility studies to explore various approaches to the development of interdisciplinary programs that offer potential solutions to problems of special significance to the mission of the NIH. These exploratory studies may lead to specialized or comprehensive centers. Substantial Federal programmatic staff involvement is intended to assist investigators during performance of the research activities, as defined in the terms and conditions of award.

Training

The National Research Service Award (NRSA) is the major mechanism for providing long-term, stable support for a wide range of promising scientists and research clinicians. Fiscal year 2001 NRSA expenditures totaled \$57,927,000, accounting for 1.5 percent of the NCI budget.

F31 Predoctoral Individual National Research Service Award

Predoctoral Individual National Research Service Awards (F31s) provide predoctoral individuals with supervised research training in specified health and health-related areas leading toward the research degree (e.g., Ph.D.).

F32 Postdoctoral Individual National Research Service Award

Postdoctoral Individual National Research Service Awards (F32s) provide postdoctoral research training to individuals to broaden their scientific background and extend their potential for research in specified health-related areas.

F33 National Research Service Award for Senior Fellows

National Research Service Awards for Senior Fellows (F33s) provide opportunities for experienced scientists to make major changes in the direction of research careers, broaden scientific background, acquire new research capabilities, enlarge command of an allied research field, or take time from regular professional responsibilities for increasing capabilities to engage in health-related research.

T32 Institutional National Research Service Award

Institutional National Research Service Awards (T32s) support training opportunities at the predoctoral or postdoctoral level at qualified institutions. Applicants must have the staff and

facilities for the proposed program. After the award is made, the institution's training program director is responsible for selecting the trainees and for administering the program. This program does not support residencies.

T36 MARC Ancillary Training Activities (Grant)

Minority Access to Research Careers (MARC) Ancillary Training Activities Grants (T36s) increase the number of well-trained minority scientists in biomedical disciplines and to strengthen the research and teaching capabilities of minority institutions. The NCI cofunds these grants with the National Institute of General Medical Sciences.

APPENDIX II

Receipt, Review, and Award Cycles

(http://grants.nih.gov/grants/funding/phs398/section_2.html#number)

Receipt, Review, and Award Cycles			
Types of Applications	Cycle I	Cycle II	Cycle III
Application Receipt Dates			
Institutional National Research Service (NRSA) Awards All new, competing continuations, supplements and revised applications	January 10	May 10	September 10
Academic Research Enhancement Award (AREA) (All new, competing continuations, and revised applications)	January 25	May 25	September 25
New Research Grants, Conference Grants and Research Career Awards	February 1	June 1	October 1
Program Project Grants and Center Grants All new, competing continuations, supplements and revised applications)	February 1	June 1	October 1
Interactive Research Project Grants (IRPGs)	February 15	June 15	October 15
Competing Continuation and Supplemental Grants Revised Research and Conference Grants, Research Career Awards	March 1	July 1	November 1
Small Business Innovation Research (SBIR), Small Business Technology Transfer (STTR) Grants (All new, supplements, and revised applications)	April 1	August 1	December 1
AIDS-Related Grants (All new, competing continuations, supplements and revised applications)	May 1	September 1	January 2
Review and Award Schedule			
Scientific Merit Review	June–July	October–November	February–March
Advisory Council Review	September–October	January–February	May–June
Earliest Project Start Date	December	April	July

Note: Several Institutes/Centers use only one or two of the receipt dates for institutional NRSA awards. Please check the program announcement, which is available at <http://grants.nih.gov/training/nrsa.htm>.

For specialized grant applications, consult with the appropriate PHS awarding component prior to the preparation of an application.

APPENDIX III

Glossary of Terms for Human Subject Requirements

(<http://www.vrc.nih.gov/ncn/clinical/decisiontrees/hsgloss.htm>)

Decision Tree

How to Write a Human Subjects Application

Terms Defined:

American Indian or Alaska Native

Analysis

Assurance, Institutional Assurance of
Protection for Human Subjects

Black or African American

Certification, IRB

Child

Clinical Research

Clinical Trial

Clinical Trial NIH-Defined Phase III

Exemption Categories

Gender

Hispanic or Latino

Human Subject

Human Subjects Concern

IRB Certification

Institutional Assurance of Protection for
Human Subjects

Majority Group

Minimal Risk

Minority Group

Native Hawaiian or Other Pacific Islander

NIH-Defined Phase III Clinical Trial

Outreach Strategies

Racial and Ethnic Categories

Scientifically Acceptable or Unacceptable

Significant Difference

Subpopulations

Valid Analysis

White

Women, see Gender

American Indian or Alaska Native

A person having origins in the original peoples of North, Central, or South America who maintains tribal affiliation or community.

Analysis

NIH requirements for analysis plans depend on the type of research proposed. They may include monitoring to detect and address adverse effects of the research as well as the ability to detect intervention differences among different types of human subjects, for example women and minorities, ethnic or racial subgroups, and children. Requirements also differ depending on the risk and complexity of the study and the probability of finding differences in the intervention effect for participant subgroups. For grantees, renewal applications (as well as contract proposals) must include the results of such subgroup analyses. See also valid analysis.

Asian

A person having origins in the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Assurance, Institutional Assurance of Protection for Human Subjects

See Institutional Assurance of Protection for Human Subjects.

Black or African American

A person having origins in the black racial groups of Africa. “Haitian” or “Negro” can be used in addition to “Black” or “African American.”

Certification, IRB

See IRB Certification.

Child

A person under age 21.

Clinical Research

Research conducted on human subjects or on material of human origin identifiable with the source person. Policy covers large and small-scale, exploratory, and observational studies. There are three types:

1. Patient-oriented research -mechanisms of disease, therapeutic interventions, clinical trials, development of new technologies
2. Epidemiologic and behavioral studies
3. Outcomes research and health services research

Training grants (T32) are exempt, but all projects to which trainees are assigned must comply with policies on inclusion of women and minorities.

Clinical Trial

For applications submitted to NIH, a prospective study of human subjects designed to answer questions about biomedical or behavioral interventions, e.g., drugs, treatments, devices, or new ways of using known treatments, to determine whether they are safe and efficacious.

Phase I tests a new biomedical or behavioral intervention in a small group of people (20-80) for the first time to evaluate its safety, e.g. determine a safe dosage range and identify side effects.

Phase II studies the intervention in a larger group of people, usually several hundred, to determine efficacy and further evaluate safety.

Phase III studies the efficacy of the intervention in large groups of several hundred to several thousand subjects by comparing it to other standard or experimental interventions monitoring adverse effects, and collecting information that will allow the intervention to be used safely.

NIH-Defined Phase III Clinical Trial is a broadly based, prospective investigation, including community and other population-based trials, usually involving several hundred or more people, to evaluate an experimental intervention in comparison with a standard or control or to compare two or more existing treatments. Often the aim is to provide evidence for changing policy or standard of care. It includes pharmacologic, non-pharmacologic, and behavioral interventions for disease prevention, prophylaxis, diagnosis, or therapy.

Phase IV done after the intervention has been marketed, monitors effectiveness of the approved intervention in the general population and collects information about adverse effects associated with widespread use.

Exemption Categories

The six categories of research that qualify for exemption from coverage by the regulations are:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on instructional strategies, or on instructional techniques, curricula, or classroom management methods.
2. Research using cognitive, diagnostic, aptitude, and achievement educational tests, surveys, interviews, or observations of public behavior, unless human subjects are identifiable and disclosure of the responses outside the research could reasonably place the subjects at risk of liability or be damaging to their financial standing, employability, or reputation.
3. Research using cognitive, diagnostic, aptitude, and achievement educational tests, surveys, interviews, or observations of public behavior that is not exempt if the subjects are public officials or candidates for public office or federal statutes require that the confidentiality of identifiable information will be maintained.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if the sources are publicly available or the information is recorded so that subjects cannot be identified.
5. Research and demonstration projects conducted or approved by agency heads to study public benefit or service programs; procedures for obtaining benefits or services or other changes to those programs.
6. Taste and food quality evaluation and consumer acceptance studies a) in wholesome foods without additives or b) in food containing a food ingredient at or below the level and use found to be safe, or agricultural chemical or environmental contaminant at or below the level deemed safe by FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Gender

The classification of research subjects into women and men. In some cases, gender cannot be accurately determined (e.g., pooled blood samples).

Hispanic or Latino

A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can also be used.

Human Subject

A living person with whom an investigator directly interacts or intervenes or obtains identifiable, private information. Regulations apply to human organs, tissues, body fluids, and recorded information from identifiable people.

Human Subjects Concern

Any actual or potential unacceptable risk or inadequate protection against risk to human subjects.

IRB Certification

Documentation from your Institutional Review Board that it has approved your research protocol, consent form (if applicable), monitoring and reporting procedures, and plans for analyzing intervention differences among different types of human subjects, for example women and minorities, ethnic or racial subgroups, and children. The IRB also approves your research annually with the noncompeting grant application and any time there are major changes in the research protocol or other procedures. The IRB must also certify its approval of the results of subset analyses in renewal applications and contract proposals. Registration with the Office of Human Research Protections, DHHS, is required for IRBs and (international research) Independent Ethics Committees (IECs) designated under an OHRP Federalwide Assurance of Protection for Human Subjects. See also Institutional Assurance of Protection for Human Subjects.

Institutional Assurance of Protection for Human Subjects

A document filed with the HHS Office for Human Research Protections (OHRP) formalizing the research institution's commitment to protect human subjects in its federally supported research. The OHRP has developed a new, simplified process for obtaining a Federalwide Assurance (FWA) of Protection for Human Subjects, applicable to all federal agencies. In the future, only the FWA will be accepted, although the deadline when it will replace other more limited assurances (e.g. the special project assurance for a specific research project) has been indefinitely extended. See also IRB certification.

Majority Group

White, not of Hispanic origin; a person having origins in the original peoples of Europe, North Africa, or the Middle East.

Minimal Risk

The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. See the official regulations for more information at Section 46.102(i).

Minority Groups

A subset of the U.S. population distinguished by either racial, ethnic, or cultural heritage. Categories are: American Indian or Alaskan Native; Asian; Black or African American, Hispanic or Latino; Native Hawaiian, or other Pacific Islander. Applications and proposals should describe subgroups to be included. Inclusion should be determined by the scientific questions under examination and their relevance to racial or ethnic groups; not every study will include all minority groups or subgroups.

NIH-Defined Phase III Clinical Trial

See Clinical Trial. NIH-Defined Phase III.

Native Hawaiian or Other Pacific Islander

A person having origins in the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

Outreach Strategies

Efforts by investigators and their staff to recruit and retain populations of interest into research studies. Such efforts should represent a thoughtful and culturally sensitive plan of outreach and generally involve other people and organizations relevant to the populations and communities of interest, e.g., family, religious organizations, community leaders, and public and private and organizations. The objective is to establish communication and cooperation to build mutual trust.

Racial and Ethnic Categories

Defined by the Office of Management and Budget Directive No. 15 and used by NIH to allow comparisons to national databases.

Scientifically Acceptable or Unacceptable

A determination based on whether proposed gender or minority representation conforms with NIH guidelines pertinent to the scientific purpose and type of study. A determination of unacceptable by the review panel bars the funding of an application or proposal until NIH staff resolve the issue. In addition, the definition changes if the research is a clinical trial as opposed to merely being clinical research.

Six Human Subjects Points

The six human subjects points were formerly part of the PHS 398 grant application instructions, but the instructions have been changed. Please see the updated [How To Write a Human Subjects Application](#).

Significant Difference

A difference of clinical or public health importance based on substantial scientific data. This definition differs from the commonly used one, which refers to statistical significance.

Subpopulations

For each minority group, subpopulations are further defined by geographic origins, national origins, or cultural differences. There are different ways of defining and reporting subpopulation data. People assign themselves to a subpopulation through self-reporting. Mixed racial or ethnic descent also applies to subpopulations, and such combinations may have biomedical or cultural implications for the scientific question under study.

Valid Analysis

An unbiased assessment that generally yields the correct estimate of the difference in outcomes between two groups of subjects and that should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting an effect. Principal requirements for ensuring a valid analysis are: allocation of study participants of both genders and from different racial and ethnic groups to intervention and control groups by an unbiased process such as randomization, unbiased evaluation of the outcome, and use of unbiased

statistical analyses and methods of inference to estimate and compare the intervention effects among different groups. See also analysis.

White

A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Women

See Gender.

APPENDIX IV

NIH Policy for Data and Safety Monitoring

(<http://grants2.nih.gov/grants/guide/notice-files/not98-084.html>)

Release Date: June 10, 1998

P.T.

National Institutes of Health

Policy

It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

Background

A clinical trial entails a relationship between participants and investigators, both of whom must fulfill certain obligations for the effort to succeed. Participants must be fully informed of the study requirements throughout the conduct of the trial and should comply with the rigors of the research protocol or be allowed the opportunity to withdraw from participation. The investigators must protect the health and safety of participants, inform participants of information relevant to their continued participation, and pursue the research objectives with scientific diligence.

Although there are potential benefits to be derived from participation in clinical research, the IRBs and the NIH must ensure, to the extent possible, the safety of study participants, that they do not incur undue risk and that the risks versus benefits are continually reassessed throughout the study period.

With this issuance, the NIH reaffirms the 1979 policy (NIH GUIDE, Volume 8, No. 8, June 5, 1979) developed by the NIH Clinical Trials Committee. Among its recommendations was the concept that "every clinical trial should have provision for data and safety monitoring." The Committee further acknowledged that "a variety of types of monitoring may be anticipated depending on the nature, size, and complexity of the clinical trial. In many cases, the principal investigator would be expected to perform the monitoring function."

In 1994, the Office of Extramural Research established the Committee on Clinical Trial Monitoring to review the oversight and management practices of the ICs for phase III clinical trials. One of the outcomes of this Committee's review was a strong recommendation that "all trials, even those that pose little likelihood of harm, should consider an external monitoring body." This policy affirms the Committee's recommendations concerning DSMBs.

Principles of monitoring data and safety

All clinical trials require monitoring—Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III); etc.

Monitoring should be commensurate with risks—The method and degree of monitoring needed is related to the degree of risk involved. A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be concluded successfully. Risk associated with participation in research must be minimized to the extent practical.

Monitoring should be commensurate with size and complexity. Monitoring may be conducted in various ways or by various individuals or groups, depending on the size and scope of the research effort. These exist on a continuum from monitoring by the principal investigator or NIH program staff in a small phase I study to the establishment of an independent data and safety monitoring board for a large phase III clinical trial.

Practical and Implementation Issues

Oversight of Monitoring

This policy provides each IC with the flexibility to implement the requirement for data and safety monitoring as appropriate for its clinical research activities. Thus, IC staff may either conduct or sponsor the monitoring of data and safety of ongoing studies or delegate such responsibilities to a grantee or contractor. Oversight of monitoring activities is distinct from the monitoring itself and should be the responsibility of the IC regardless of whether the monitoring is performed by NIH staff or is delegated. Oversight of monitoring must be done to ensure that data and safety monitoring plans are in place for all interventional trials, that the quality of these monitoring activities is appropriate to the trial(s), and that the IC has been informed of recommendations that emanate from monitoring activities.

Institutes' and Centers' Responsibilities

Though ICs may perform a variety of roles in data and safety monitoring and its oversight, the following are the minimum responsibilities of sponsoring ICs.

- Prepare or ensure the establishment of a plan for data and safety monitoring for all interventional trials.
- Conduct or delegate ongoing monitoring of interventional trials.
- Ensure that monitoring is timely and effective and that those responsible for monitoring have the appropriate expertise to accomplish its mission.
- Oversee monitoring activities.
- Respond to recommendations that emanate from monitoring activities.

Performance of Data and Safety Monitoring

The ICs will ensure the integrity of systems for monitoring trial data and participant safety, although they may delegate the actual performance to the grantee or contractor. Monitoring must be performed on a regular basis, and conclusions of the monitoring reported to the IC. Recommendations that emanate from monitoring activities should be reviewed by the responsible official in the IC and addressed. The ICs also have the responsibility of informing trial investigators concerning the data and safety monitoring policy and procedures. Considerations such as who shall perform the monitoring activities, the composition of the monitoring group (if a group is to be used), the frequency and character of monitoring meetings (e.g., open or closed, public or private), and the frequency and content of meeting reports should

be a part of the monitoring plans. IRBs should be provided feedback on a regular basis, including findings from adverse-event reports, and recommendations derived from data and safety monitoring.

Monitoring activities should be conducted by experts in all scientific disciplines needed to interpret the data and ensure patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available if warranted.

Ideally, participants in monitoring outcomes of a trial are in no way associated with the trial. For trials that are conducted as part of a cooperative group, a majority of the individuals monitoring outcome data should be external to the group. ICs should require policies that evaluate whether the participants have conflicts of interests with or financial stakes in the research outcome; and when these conflicts exist, policies must exist to manage these in a reasonable manner.

Generally, data and safety monitoring boards meet first in open session, attended by selected trial investigators as well as NIH program staff or project officers and perhaps industry representatives, and then in closed session where they review emerging trial data. When “masked” data are presented or discussed, no one with a proprietary interest in the outcome should be allowed. Participants in the review of “masked” or confidential data and discussions regarding continuance or stoppage of the study should have no conflict of interest with or financial stake in the research outcome. However, if there is an open session, they could be present.

Confidentiality must be maintained during all phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations. Besides selected NIH program staff, other key NIH staff, and trial biostatisticians, usually only voting members of the DSMB should see interim analyses of outcome data. Exceptions may be made under circumstances where there are serious adverse events, or whenever the DSMB deems it appropriate.

Individuals or groups monitoring data and safety of interventional trials will perform the following activities:

- Review the research protocol and plans for data and safety monitoring.
- Evaluate the progress of interventional trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome. Monitoring should also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.
- Make recommendations to the IC, IRB, and investigators concerning continuation or conclusion of the trial(s).
- Protect the confidentiality of the trial data and the results of monitoring.

Examples of Monitoring Operations

The following provides examples of appropriate types of monitoring and oversight for different types of studies. These are illustrative only. The ICs must develop and implement monitoring activities and oversight of those activities appropriate to the study, population, research environment, and the degree of risk involved.

Phase I: A typical phase I trial of a new drug or agent frequently involves relatively high risk to a small number of participants. The investigator and occasionally others may have the only relevant knowledge regarding the treatment because these are the first human uses. An IC may require the study investigator to perform continuous monitoring of participant safety with frequent reporting to IC staff with oversight responsibility.

Phase II: A typical phase II trial follows phase I studies, and there is more information regarding risks, benefits and monitoring procedures. However, more participants are involved, and the toxicity and outcomes are confounded by disease process. An IC may require monitoring similar to that of a phase I trial or supplement that level of monitoring with individuals with expertise relevant to the study who might assist in interpreting the data to ensure patient safety.

Phase III: A phase III trial frequently compares a new treatment to a standard treatment or to no treatment, and treatment allocation may be randomly assigned and the data masked. These studies usually involve a large number of participants followed for longer periods of treatment exposure. While short-term risk is usually slight, one must consider the long-term effects of a study agent or achievement of significant safety or efficacy differences between the control and study groups for a masked study. An IC may require a DSMB to perform monitoring functions. This DSMB would be composed of experts relevant to the study and would regularly assess the trial and offer recommendations to the IC concerning its continuation.

APPENDIX V

Answers to Frequently Asked Questions about NIH Grants

(<http://grants1.nih.gov/grants/funding/giofaq.htm>)

Abstracts?

Abstracts are allowed in the appendix of an application. Up to 10 publications, manuscripts (accepted for publication), abstracts, patents, and other printed materials directly relevant to the project may be included.

Appendix?

Each page in the appendix may be double-sided.

The appendix will be distributed to the primary and the secondary reviewers of the application assigned within the study section. One copy of the appendix is forwarded to the assigned NIH institute's program administrator, and one copy remains with the Scientific Review Administrator (SRA) until the review is complete.

Assurance Forms—Civil Rights, Human Subjects & Animal Welfare?

Civil Rights: Before a grant award can be made, a domestic applicant organization must certify that it has filed the DHHS Office for Civil Rights and Assurance of Compliance (Form HHS 690) pertaining to four non-discrimination requirements. This form is required to be submitted only once by an institution; it may be obtained from grantsinfo@nih.gov or by telephone at 301-435-0714.

As a condition of receiving NIH Support, an applicant organization must certify compliance with a number of assurances. Most assurances and certifications are incorporated by reference in the PHS 398 application kit (see pp.27-36). For those assurances, the signature on the application face page of the duly authorized representative of the applicant institution certifies that the applicant organization will comply. The inclusion of human subjects or animals in research requires special certifications as described below.

Human Subjects: The Federal Policy (Common Rule) for the protection of human subjects at Section 103(a) requires that each institution “engaged” in federally supported human subject research file an “Assurance” of protection for human subjects. The Assurance formalizes the institution's commitment to protect human subjects. The requirement to file an Assurance includes both “awardee” and collaborating “performance site” institutions. For additional information and guidance, please visit the Office for Human Research Protections (OHRP) web site at: <http://ohro.osophs.dhhs.gov/>.

Animal Welfare: Research involving human and/or animal subjects must comply with the HHS regulations for the Protection of Human Subjects (45 CFR 46) and/or the PHS Policy on Humane Care and Use of Laboratory Animals. Institutions without an applicable Assurance of Compliance on file with the Office of Laboratory Animal Welfare (OLAW) must provide an appropriate Assurance prior to funding. For additional information and guidance, please visit the OLAW web site at: <http://www.grants.nih.gov/grants/olaw/olaw.htm>.

Award Data?

NIH award data is accessible on the NIH web site at: <http://www.grants.nih.gov/grants/award/award.htm>. This site provides reports, charts and graphs, extramural trends, listings of awards arranged geographically by state, city, and grantee organization within the city and other award-related information.

Center for Scientific Review (CSR)

The Center for Scientific Review (CSR) is the new organizational name of the former Division of Research Grants (DRG). CSR is the central NIH organization that receives grant applications; creates a new computer record for each; assigns applications to initial review groups as well as to potential funding units of NIH and other cooperating health research agencies; and conducts peer review of grant applications. For more detailed information, please see the web site <http://www.csr.nih.gov/> and the section on peer review. At that site there is also an excellent overview of the NIH peer review and award process.

Citations?

Citations may **not** be scattered throughout the Research Plan of an application. They should be put in Section G, Literature Cited.

Collaborators/Consultants?

A **collaborator** is an individual involved with the principal investigator in the scientific development or execution of the project. These individuals would typically devote a specific percent of effort to the project and would be identified as key personnel. The collaborator may be employed by, or affiliated with, either the grantee organization or an organization participating in the project under a consortium or contractual agreement.

A **consultant** is an individual who provides professional advice or services on the basis of a written agreement for a fee. These individuals are not normally employees of the organization receiving the services.

NOTE: A biographical sketch (Form FF) is required for all key personnel. Collaborators and consultants should be included only when their level of involvement on the grant meets the key personnel definition and each biographical sketch must be no more than four pages.

Concurrent Applications?

Submission of more than one application within the same review cycle is permissible for some, but not all, award mechanisms:

For a NRSA Fellowship (F series), only one application may be submitted in the same review cycle.

For an investigator-initiated grant (R01), small grant (R03), career development award (K-Series, excepting K08), small business innovation research grant (SBIR), small business technology transfer grant (STTR), or a conference grant (RI3), more than one application in the same review cycle may be submitted, if each application describes a different research topic.

An application for an investigator-initiated grant (R01) for support of the same research proposed as a subproject within an application for a program project grant (P01), or as a subproject within an application for other P-series grants, such as *P30* or *P50*, may be submitted in the same cycle.

Copies?

Photocopies of blank application forms may be used as original forms for grant preparation.

Instructions for the number of copies of research grant applications and appended materials to be submitted at the regular application receipt dates are detailed on page 21 of the PHS 398 instructions. There may be additional instructions for submission of responses to Requests for Applications (RFAs) in the NIH Guide announcements of RFAs.

Delivery of Applications?

All applications and other deliveries to the Center for Scientific Review must either come via courier delivery or the USPS. Applications delivered by individuals to the Center for Scientific Review will no longer be accepted.

For additional information, see the NIH Guide Notice (Nov. 13, 2001)
<http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-02-012.html>.

Eligibility?

In general, any organization is eligible to apply for regular NIH research grants, such as R01 grants and other grant mechanisms. The applicant is the research organization, although a principal investigator (PI) writes the research proposal; and if a grant is awarded, the grantee is the organization that submitted the application. For some specific programs there may be special eligibility requirements, and those requirements are detailed in the Program Announcement (PA) or Request for Applications (RFA) published in the NIH Guide. (See next item for access to the NIH Guide.)

Guide for Grants and Contracts?

Current and past issues of the NIH Guide may be accessed from the NIH web site under the category of Funding Opportunities at <http://www.grants.nih.gov/grants/oer.htm> or a Table of Contents Email version of the NIH Guide may be obtained by subscription to the NIH Listserv. To subscribe to the Table of Contents, send an Email message to <mailto:%20listserv@list.nih.gov> in which the text of the mail should read ONLY: SUBSCRIBE NIHTOC- L Firstname Lastname (e.g. SUBSCRIBE NIH TOC-L Bill Jones)

The message must originate from the same address where you would like the weekly Table of Contents to be received and read, circulated or filed.

Indirect Costs?

Reimbursement for indirect costs (also called facilities and administration costs, or F&A) is allowed on most types of NIH awards. Typically, indirect cost reimbursement is calculated using the institution's indirect cost rate as negotiated with HHS. The applicant institution's office of sponsored research or business office can provide this information. If an organization does not already have an HHS-negotiated indirect cost rate, refer to the PHS Grants Policy Statement,

appendix 8, for the appropriate HHS Division of Cost Allocation office (for educational and other non-profit organizations) or PHS agency (for-profit organizations).

Introduction?

Required only on REVISED and SUPPLEMENTAL applications, the “Introduction” section of the application is not counted towards the Research Plan 25-page limit. It is separate from the Research Plan.

Investigator-Initiated Applications?

The term, Investigator-Initiated Application, means that the applicant has proposed research for funding by NIH that is not responding to any solicitation by NIH in announcements such as a Program Announcement (PA) or a Request for Applications (RF A). The research proposed by the applicant mostly likely would be related to the stated program interests of one or more of the Institutes of NIH in descriptions of their programs, but the scientist has proposed a research project that is independent of any particular solicitation by an Institute. The most frequently used mechanisms of support for such applications are the “R” series of grants, notably the R01 research project grant.

IRB & IACUC Approvals?

According to the Revised Policy for IRB Review of Human Subjects Protocols in Grant Applications, IRB approval is not required prior to NIH peer review of an application. However, no grant award can be made without IRB approval. Following NIH peer review and notification of priority score/percentile, institutions should proceed with IRB review for those applications that have not yet received IRB approval and that appear to be in a fundable range. The term “fundable range” does not signify a certainty of funding. For more information, please visit the following web site: http://www.grants.nih.gov/grants/irb_review_pol.htm.

Institutional Animal Care and Use Committee (IACUC) approval is required when animal studies are involved. Beginning with applications submitted for the October 1, 2002, receipt date (and any other receipt dates that result in applications being reviewed for May/June 2003 Councils), IACUC “just-in-time” will be in effect. That is, institutions will be permitted flexibility in the timing of IACUC review relative to submission of an application. The full NIH Guide Notice is available at: <http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-02-064.html>.

Key Personnel?

The definition of key personnel in the PHS 398 kit is “individuals who contribute in a substantive way to the scientific development or execution of the project, whether or not salaries are requested.”

Modular Grants?

The modular grant application concept establishes a size (in dollars) of module in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. In addition, an applicant will need to submit certain information only when it is highly likely that NIH will make an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers, and Institute staff. The research grant application form PHS 398 (rev. 05/01) is to be used with the instructions for the modular grant application.

Modular Grant applications request direct costs in \$25,000 modules, and may request up to \$250,000 (10 modules) for direct costs per year. Applications that request more than \$250,000 direct costs in any year must follow the traditional PHS 398 application instructions.

The NIH Modular Research Grant Application web page <http://www.grants.nih.gov/grants/funding/modular/modular.htm> can guide you to detailed information about the application process, including samples of relevant pages from an application.

Notification of Receipt?

The snap-out mailer is the only official notification from the NIH that an application has been received by the Center for Scientific Review (CSR) Referral Office. It acknowledges receipt of the application, indicates the Initial Review Group (IRG), NIH Institute assignment, and provides the Scientific Review Administrator's (SRA) name and telephone number. The snap-out mailer is sent six to eight weeks after the receipt date to the addresses provided on the application face page.

If additional proof that an application has been received is desired, the application may be hand delivered to the Rockledge Center before 5:00 p.m., Monday thru Friday, and the messenger can obtain a signature of receipt.

Omitted Information?

If information has been inadvertently omitted from a submitted application package that is critical to the receipt and assignment of the application, e.g., the face page or reference letters, the applicant should call the Center for Scientific Review (CSR) Referral Office at (301) 435-0715. Otherwise, the applicant should wait for receipt of the snap-out mailer (about six to eight weeks after the receipt date), and then contact the Scientific Review Administrator (SRA) identified on the mailer.

Other Support?

According to the PHS 398 Instructions, "Other support information is required for all applications that are to receive grant awards; however, NIH will request complete and up to date "other support" information from applicants at an appropriate time after peer review. The institute's scientific program and grants management staff will review this information prior to award."

Page Numbering?

The pages must be numbered with consecutive integers. If a continuation page is necessary for one of the pre-numbered forms pages, the requirement for consecutive integer numbering of the whole application takes precedence.

Do not include "subpages" to the form pages in the kit (i.e., do not number the pages as 4, 4a, 4b, 5).

Photographs?

Glossy photographs or color images that are represented in the Research Plan may be included in the appendix with the original application. DO NOT paste photographs in application.

Graphs, diagrams, tables, and charts not needed in a glossy format to show detail must be included with the Research Plan and may NOT be included in the appendix.

Do NOT use the appendix to circumvent the page limitations of the Research Plan.

PHS 398 Application Kits?

Beginning January 10, 2002, applicants are required to use the revised (05101 forms). The revised PHS 398 and PHS 2590 instructions are only available online at <http://www.grants.nih.gov/grants/forms.htm>. Applicants are encouraged to access the instructions and forms via the Internet because they provide valuable links to current policy documents and allow easy navigation of the instructions.

PHS 398 application kits cannot be faxed to applicants.

PHS 416 Application Kits?

The revised Ruth L. Kirschstein Individual National Research Service Award Application (PHS 416-1) and Progress Report for Continuation Support (PHS 416-9) are available online in a fillable format at: <http://www.grants.nih.gov/grants/fonns.htm>. NOTE: For the April 2003 application receipt date and beyond, use of the new version Rev. 6/02 is required.

Programs?

For general information about NIH research and research training programs, interested parties may contact grantsinfo@nih.gov.

Information about the programs of a specific NIH institute can be found on the NIH website: <http://www.nih.gov/>. Click on Institutes and Offices. Also the NIH Extramural Programs describes the programs of the NIH and includes contacts for additional information at the website: <http://www.grants.nih.gov/grants/funding/funding.htm>.

Each Program Announcement (PA) and Request for Applications (RFA) in the NIH Guide for Grants and Contracts includes contact information for the grants management officer and program administrator for additional information about that PA or RFA.

Program Announcement (PA)?

To obtain a specific program announcement, consult the NIH Guide for Grants and Contracts on the OER website, <http://www.grants.nih.gov/grants/oer.htm> or contact the Institute that issued the program announcement. The NIH Guide has a numerical list of the program announcements.

Program Project Grants (P01)?

Each of the NIH institutes that use P01s publishes its own guidelines for program project (P01) applications. For answers to questions regarding program project grants, applicants are encouraged to contact the NIH institute most likely to fund their project. Occasionally, an Institute's solicitation published in the NIH Guide will specify that a program project is the funding mechanism appropriate for a grant application in response to the announcement.

Receipt Dates?

The PHS application documents (i.e., PHS 398, PHS 416-1) contain the receipt dates that apply to grant applications unless special receipt dates have been specified in either a program announcement (PA), request for application (RF A), or program guidelines published in the NIH Guide for Grants and Contracts. A list of receipt dates is available from Grants info (301-435-0714) by choosing Option 3 on the menu. Receipt date schedules are also posted on the NIH website: <http://www.grants.nih.gov/grants/funding.htm> under the category of Receipt Dates.

WHENEVER A RECEIPT DATE FALLS ON A WEEKEND OR HOLIDAY, THE APPLICATION IS DUE ON THE FOLLOWING BUSINESS DAY. This applies to postmark dates as well.

Unsolicited Applications. An unsolicited application is considered on time if it is:

- a. received by the published receipt date or,
- b. mailed on or before the published receipt date and a proof of mailing is provided.

Proof of mailing may be either a dated receipt from a commercial carrier or the US Postal Service, or a legible US Postal Service postmark. (Private meter postmarks are not acceptable.) This policy also applies to unsolicited AIDS-related applications and to Academic Research Enhancement Award (AREA) applications. Unsolicited applications, with the exceptions of SBIR and STTR, are those submitted on the standard receipt dates stated in the grant application forms instruction books and in the table of receipt dates posted on the NIH website above.

Solicited Applications. A solicited application or proposal must be received by the date specified in the request for applications (RF A) or program announcements with special receipt dates (PAR). However, an application received after the deadline may be acceptable if it carries a legible proof-of-mailing date assigned by the carrier that is AT LEAST ONE WEEK prior to the deadline date. Solicited applications include those submitted in response to RFAs; program announcements with special receipt dates (PARs); or solicitations for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) applications.

Reference Letters?

In an application for a Fellowship Award (F32), or for selected Research Career Development Awards (see instructions for the K series of awards), three sealed, reference letters must be submitted with the application. If fewer than three letters are submitted with the application, the application will be returned to the applicant.

The sealed envelopes should clearly indicate the application to which they belong, in case they are inadvertently separated from the application. It is not necessary to designate a person to receive them.

The sealed letters **must** be attached to the front of the original application and included in the package with the original application and the copies.

Resubmitted Applications?

See Revised/Amended Applications.

Review Schedules?

For peer review and award schedules of grants, refer to the application instruction books, {PHS 398, PHS 416-1}, program announcements (PAs), requests for applications (RFAs), and program guidelines. Schedules depend upon the type of application submitted. Review and award cycle schedules are also posted on the NIB website:

<http://www.grants.nih.gov/grants/funding/funding.htm> and click on Receipt Dates.

Revised/Amended versus Renewal Application?

A revised/amended application is one that has been modified in response to the critique in the summary statement of an application that was previously reviewed, but not funded. (“revised” and “amended” applications are synonymous.)

A competing “renewal” is a grant for additional funds and period of award.

A revised/amended application or an application for a competing “renewal” is made on the same PHS application form used for the initial grant or fellowship.

An application for an R01 grant submitted in response to a request for application (RFA) and not funded may be resubmitted as an unsolicited application. However, it must be submitted as a revised/amended application and include the changes made in response to the critique of the original submission.

Salary Cap?

Effective January 1, 2002, the Executive Level I salary level increased to \$166,700.

The full announcement on Salary Limitation is available at:

<http://www.grants.nih.gov/grants/guide/notice-files/NOT-OD-02-030.html>. For additional guidance, please contact the Grants management Office of the NIB institute most likely to fund your application.

Sample Applications?

Sample applications that have been funded are not available from central NIH sources. However, occasionally the NIH Guide announces regional seminars for assistance in grant preparation.

Applicants may also find it helpful to ask advice from an experienced investigator and to contact the NIH administrator of the program most likely to fund their application.

Scientific Areas Funded by NIB?

Several resources exist to determine the areas of research types, and levels of funding:

NIH Guide for Grants and Contracts issues Program Announcements (PAs) for ongoing programs as well as Requests for Applications (RFAs) in various scientific areas. The NIH Guide is published weekly on the OER web site, <http://www.grants.nih.gov/grants/oer.htm>.

Computer Retrieval of Information on Scientific Projects (CRISP) provides a brief description and the administrative data of each funded NIH research project. CRISP is updated quarterly on the OER Website. CRISP does not include amounts awarded on the grants.

NIH Extramural Programs, a publication available electronically, outlines all ongoing NIH extramural research and research training programs. This resource also describes various information clearinghouses that provide information to the public on health and disease. It is available at the NIH website, <http://www.grants.nih.gov/grants/funding/funding.htm>.

Scientific Review Administrator (SRA)?

The scientific review administrator (SRA) is the designated federal official responsible for the administration of a study section which conducts the initial peer review of applications. This individual compiles a summary statement for each application upon the completion of the initial review.

Signatures?

Original signatures are required on the original face page of the application, but not on the copies.

SRG and IRG?

A scientific peer review group (SRG) is the generic functional term for any group engaged in scientific and technical peer review. SRGs may be individually chartered or they may be part of a larger chartered group (i.e., IRG). SRGs are commonly called study sections in CSR (formerly DRG) and are called review committees in the institutes and centers of NIH that have their own specialized peer review groups. An IRG (initial review group) is a cluster of SRGs with related scientific focus chartered as a single entity.

Study Section Assignment?

Applications are assigned to the most appropriate initial review group (IRG)—please see definitions of “IRG” and “SRG” under the SRG heading above—on the basis of the scientific emphasis of the application and the NIH Referral Guidelines. The assignments are made by NIH Referral Officers, senior science administrators who have had research and scientific review administrator experience. An applicant may suggest, in a cover letter, up to three study sections considered appropriate to review the application.

Study Section Members?

Members of study sections are selected by the scientific review administrators with the concurrence of their supervisors in the Center for Scientific Review (CSR). For specific information about the membership of study sections, see the website: <http://www.csr.nih.gov/committees/rosterindex.as> with member listings. Study section members are chosen for their expertise in the areas of science relevant to a particular review group, and for their ability and willingness to evaluate research grant applications. After studying the applications at home, they meet together, generally three times a year, for the purpose of reviewing the group of applications received at the latest deadline. The members serve for a period of three or four years. Recommendations of the study sections are forwarded to the funding Institutes of NIH where funding decisions are made for each of the grant applications.

A federal employee may serve as a study section member. However, most of the members of the study sections are researchers from universities and other research organizations throughout the United States. Applicants should not contact study section members directly. Contact the Scientific Review Administrator instead.

Study Section Rosters?

Rosters of the Center for Scientific Review (CSR) (formerly known as the Division of Research Grants- DRG) study sections are available electronically. They can be accessed from the CSR web site, <http://www.csr.nih.gov/> that also has descriptions of the scientific areas covered by each study section.

Supplements?

There are two types of supplements: Administrative and Competitive.

Administrative supplement: NIH awards additional funding to an existing grant to cover additional expenses within the scope of the existing award.

For example: The supplements to train a minority research student or a student with disabilities are administrative supplements. It is awarded “administratively:” the application does not require review by a study section or national advisory council, nor does an applicant compete for this funding with other applicants.

Competitive supplement: The applicant competes for additional funding to expand the scope of the existing grant, requiring additional personnel, equipment, and/or other expenses. A competitive supplement application must be peer reviewed.