

Last updated on 24th August, 2001

# Center for Scientific Review

National Institutes of Health

## Referral & Review

### A Straightforward Description of What Happens to Your Research Project Grant Application (R01/R21) After it is Received for Peer Review

*NOTE: There exists a great deal of official documentation of the rules and regulations governing the conduct of NIH peer review. What follows is meant to be a simpler snapshot of the process for applications reviewed in the Center for Scientific Review (formerly the Division of Research Grants).*

On a major grant application receipt day, delivery trucks unload thousands of packages containing grant applications at the loading docks of the [Rockledge 2 Building](#), the home of the NIH Center for Scientific Review (CSR). Each package is opened; the application is date-stamped and logged into the NIH database for tracking.

Over a dozen Referral Officers review the contents of some 10,000 applications each grant cycle and, using written guidelines, decide first which [Integrated Review Group](#) (IRG) would be most appropriate for assessment of scientific merit. IRGs are clusters of study sections that review similar science. Once the IRG is identified, the application is then assigned to one of the constituent study sections within the IRG. In addition to the IRG assignment, Referral Officers also identify which Institute(s)/Center(s) (I/C) of the NIH would be most suitable to fund the application, should it be considered sufficiently meritorious. Once the I/C is identified, a unique [application number](#) is assigned to each application. The Referral Office seriously considers written requests from applicants for both study section and Institute assignments (just include a cover letter with the application). The assignment process is a collegial one, with interaction, when necessary, on a case-by-case basis among Referral Officers, study section [Scientific Review Administrators \(SRAs\)](#), Institute program representatives, and applicants.

Within 10 days of the completion of application assignment, a computer-generated letter is mailed to each applicant and sponsored research office, listing the [study section](#) and potential funding Institute. Upon receipt of this notice, applicants can question the study section or I/C assignments by contacting either the [study section SRA](#) or the Referral Office (301-435-0715) . There are official guidelines defining the content and boundaries of the science reviewed in each study section, but there is overlap in the science reviewed by the various study sections. Indeed, because of the broad scope of today's research projects, often a particular application may be appropriate for more than one of the study sections, and CSR staff attempt to refer the application to the single most appropriate committee. The referral of all 10,000 applications for a given review round may take up to six weeks. If applicants have not received notification at that time, they should contact the Referral Office.

As applications are assigned to a study section, the SRA begins to read through them, analyzing content, checking for completion, and deciding which study section members would be best suited to review each application, or act as discussants. Approximately six weeks before the study section meeting, packages are mailed to members which include all of the applications to be reviewed at the meeting (with the exception of those applications for which a particular member is in conflict.) Typically, two or three members are assigned to provide written reviews of each application, and one or two additional members to serve as discussants.

NOTE: A chartered CSR study section is composed generally of 18 to 20 individuals, nominated by the SRA from among the active and productive researchers in the biomedical community, to serve for multi-year terms. The goal is to have the group's combined knowledge span the diversity of subject matter assigned to the study section for review. However, this is difficult to accomplish, and the study section's membership is frequently supplemented by temporary members and written outside opinions. In some instances, Special Emphasis Panels (SEPs) are formed on an ad-hoc basis to review applications requiring special expertise, or due to special circumstances (such as when a conflict of interest occurs).

Because of the multi-month period between submission and review of an application, applicants often wish to submit supplementary materials. However, each study section has policies for acceptance of such additional material (e.g. length; time of submission). SRAs should be contacted prior to submission, both as an alert for the SRA, and to ascertain acceptable content, format, and deadline.

One week before the convening of a study section, the SRA solicits, from all members, a list of R01 applications believed not to rank in the top half for scientific merit. The individual lists are coalesced, and a final list is established at the outset of the study section meeting. Those R01 applications in the lower half are considered to be "[streamlined](#)". They are not scored or discussed at the meeting, but reviewers' written critiques are provided, and the applicant may subsequently revise and resubmit the application. "Streamlining" is not equivalent to disapproval, but rather represents a decision by the study section that the application would not rank in the top half of applications generally reviewed by that study section.

With some minor variations, all regular CSR study section meetings follow the same format. The meetings usually last two days. Members convene around a conference table to maximize interaction. The chairperson (a member of the study section) and the SRA sit together and are responsible for jointly conducting the meeting. Representatives from the various NIH Institutes) are encouraged attend, but must sit in chairs set back from the conference table

and may not participate in the discussions. After the assigned reviewers and discussants provide their evaluations, any outside opinions are read. After general discussion, members mark their priority scores privately for each application on scoring sheets provided by the SRA. These sheets are collected by the SRA or an administrative assistant at the conclusion of the meeting.

Within a few days after the meeting, all priority score information is entered into the application database. Computer generated priority scores and percentiles are then automatically mailed to applicants.

Feedback to applicants is important. However, it requires approximately six weeks to generate an average of 80 summary statements. Once summary statements are produced and transmitted to the appropriate NIH Institute for funding consideration, the SRA's control over the review of those applications ends, and his/her attention turns to the next grant application cycle. At this junction, it is the Institute program officials who become the applicant's link to the NIH with regard to interpretation of the reviews and the disposition of the application.

There is a flow to the review process, repeated cycle after cycle. For example, applications submitted for the October/November receipt dates will be assigned to CSR study sections by early December, and sent out to members of the study section for scientific review in late December/January.

Study sections meet between mid-February and mid-March, and summary statements are prepared by late April/May. Institute Advisory Councils, the second step in NIH peer review, meet in May/June to consider the study sections' recommendations, and successful applicants can begin to receive funding several months later.

While this introduction describes R01/R21 applications, other types of grant applications reviewed in CSR are handled in a similar manner, but there are some differences. Several types of applications (e.g. Small Business Innovation Research (SBIR) and fellowships) receive expedited review and have receipt deadlines one to two months later than R01s. Also, SBIRs are always reviewed by Special Emphasis Panels and fellowships are not "streamlined."

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Last updated on 7th April, 2004

# Center for Scientific Review

## National Institutes of Health

### Referral & Review

## Guidelines for Reviewers

The mission of the National Institutes of Health (NIH) is to improve the health of all Americans by promoting research that will help prevent, detect, diagnose, or treat disease. Peer review is the cornerstone of the NIH extramural program. As a scientific consultant participating in a study section, you are asked to evaluate the scientific merit of grant applications. The NIH sincerely appreciates your valuable role in this first step of review. The second stage of review is performed by a National Advisory Board or Council serving one of the funding institutes of the NIH and is based on the advice of the study section as well as additional criteria such as program priorities.

The Scientific Review Administrator (SRA) and the Chair of the study section work together to lead the peer-review process and are valuable sources of information when you have questions. In addition, the SRA and the Chair welcome your feedback concerning the review process. (Please see the two related documents, "Role of the SRA" and "Guidelines for Study Section Chairs")

**Examine Your Application Package Promptly:** Four to six weeks before the meeting, you will receive a package containing all of the applications except for those that pose a conflict of interest for you (see Conflict of Interest below). Included will be a list of applications on which you are expected to focus as a Reviewer or Discussant. It is critical that you promptly alert the SRA (within a few days is optimal) to unforeseen conflicts or questionable assignments concerning the matching of your expertise. Pay special attention to a letter from the SRA, which will provide information about the study section meeting including instructions and deadlines for making your travel plans.

**Conflict of Interest:** The SRA will identify conflicts of interest involving you and any application. Your assistance is necessary. Consider the following as potential conflicts: investigators are listed with whom you have a financial and/or professional relationship; the funding decision on any application would benefit you directly; you feel there may be a perception of conflict. Notify the SRA in such cases. The SRA will make the final determination. Supplying a reagent or service that is available to anyone in the scientific community does not, by itself, constitute a conflict of interest.

**Confidentiality:** The applications are to be considered confidential and it is important to respect the privacy of the investigators' ideas. If consultation with an expert is appropriate, contact the SRA who can recruit an outside opinion and secure a signed conflict of interest form.

**Expectations of Reviewers and Discussants:** Each application is assigned to at least two Reviewers and one Discussant. As a Reviewer, you will be expected to write a complete critique. As

a Discussant, you are not required to provide written comments, although you may choose to do so. The SRA may ask you for written comments if you have a special expertise or if you present views at the meeting not captured in other reviews. Although you should prioritize your efforts to evaluate the applications assigned to you, reading other applications as your time allows is highly encouraged.

**Amended and Renewal Applications:** For revised applications, your critique should include an evaluation of the changes made in response to the last review. You should consider the response by the investigator to the previous criticisms as one component in your overall evaluation of the current application. Note, however, that you are not tied to previous reviewers' critiques and can raise new criticisms and/or disagree with previous comments on strengths and weaknesses. If the application is a competing renewal, you should include an evaluation of progress over the past project period.

**The Written Critique:** Consider all aspects of the application. Do not describe the investigator's plans; rather make evaluative statements about the strengths and weaknesses based on criteria described elsewhere. A strong application will contain good ideas, address important issues, and generate confidence that the investigator(s) will make a significant impact. Do not insist on a hypothesis-driven approach if the research is sound and will move the field forward. Focus is important, especially for new investigators. Avoid emphasizing minor technical details, making tutorial comments, or redesigning the investigator's experiments. Put the requirement for preliminary data in perspective such that bold new ideas, young investigators, and risk taking are encouraged rather than stymied. Be concise; longer reviews are not necessarily better. Sample critiques are less than 2 pages long. Where possible, try to put the strengths and weaknesses in perspective by indicating their relative magnitude. Do not consider issues outside of scientific merit in your critique such as current or past funding levels or personal situations of the investigator.

**Scoring:** Priority scores range from 1.0 (highest priority) to 5.0 (lowest priority). Use your judgment in weighing the relative importance of each criterion. An application does not need to be strong in all categories to be judged likely to have a major scientific impact. For example, an investigator may propose to carry out important work that by its nature is not innovative, but is essential to move a field forward. An application of average strength relative to other applications ordinarily reviewed by the study section should receive a score of 3.0 although the scoring behavior of individual study sections may vary. It is important to note that unacceptable designations in the areas of protection of human subjects from research risk or inclusion of gender, minorities, or children should be reflected in the priority score. Be consistent and remember that you are welcome to discuss scoring issues with the SRA and/or the Chair. It may be helpful in spreading the scores to rank the applications assigned to you for any given meeting in order of scientific merit.

**Scientific Misconduct:** It is vital that you not make allegations of potential misconduct at the study section meeting or in the critique. Such concerns must be brought to the attention of the SRA in a confidential manner, preferably before the study section meets.

**Discussion of Applications:** The Study Section Chair will guide the scientific discussion, which often begins with a brief indication of enthusiasm in the form of preliminary priority scores from the assigned reviewers and discussant(s). In your review, clearly summarize your views emphasizing the major strengths and weaknesses of the application based on the criteria relevant to the grant

mechanism under review. If you are first to present, briefly describe the overall goals of the application for the benefit of other members of the study section who are less familiar with it. If you are not first to present your evaluation, integrate your views with those already presented. Avoid repeating detailed descriptions of strengths and weaknesses already provided. Identify major issues with which you disagree and raise any issues not brought up previously that you feel should influence the score of the application. It is important that you listen carefully to each presentation and be prepared to defend or change your point of view based on scientific arguments. Keep an open mind, but don't give in just to reach consensus. Do not be afraid to express your view, but avoid statements that might be considered offensive. You are strongly encouraged to participate in the discussion of applications not assigned to you. A vigorous discussion involving multiple panel members is ideal. Consensus is not a necessity and the Chair will decide when further discussion is not likely to resolve scientific differences of opinion. In such cases, it is important to establish the foundation of the disagreement. Each reviewer present for the discussion will vote on each application. Your score should be based on your level of enthusiasm. It is important, however, that you articulate any plan to give a score outside the range indicated by the assigned reviewers. Consider human subject issues, if any, before scoring. Budget recommendations are addressed after scoring followed by issues of compliance with regulations and policies regarding animals and biohazards. Please note that, in the event that your views are altered as a result of the discussion, you are encouraged to modify your written critique appropriately so that the summary statement reflects your final evaluation of the application.

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Last updated on 18th July, 2001

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National Institutes of Health

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## REVIEW OF NEW INVESTIGATOR R01s

### Guidelines for Reviewers

New investigators are important to the future of biomedical research. In order to provide new investigators maximum freedom in identifying the level and period of support needed for the work they are planning and thus enhance their opportunities to establish careers in research, NIH has announced a new policy. Under this policy, new investigators are encouraged to submit traditional research project grant (R01) applications, which will be identified as being from new investigators. First Independent Research and Transition (FIRST; R29) award applications are no longer accepted (effective June 1998). A new investigator is one who has not previously served as such on any PHS-supported research project other than a small grant (R03), an Academic Research Enhancement Award (R15), an exploratory/developmental grant (R21), or certain research career awards directed principally to physicians, dentists, or veterinarians at the beginning of their research career (K01, K08, K22, and K23). Current or past recipients of Independent Scientist and other nonmentored career awards (K02 and K04) are not considered new investigators.

New investigators are typically less experienced in the preparation of applications and expression of their research plans. To ensure fair reviews for new investigators, the NIH has revised application forms to allow new investigators to indicate this status and thus ensure that reviewers can readily identify applications that are submitted by new investigators. The biosketch should also be used to identify new investigators. All applicants should be evaluated in a manner appropriate for the present stage in their careers.

**IMPLEMENTATION:** When reviewing these applications, reviewers should keep in mind the experience of and the resources available to the new investigator. When considering an application from a new investigator the five new review criteria must be evaluated in a manner appropriate to the expectations for and problems likely to be faced by a new investigator. Specifically, when considering:

**Approach:** more emphasis should be placed on demonstrating that the techniques/approaches are feasible than on preliminary results

**Investigator:** more emphasis should be placed on their training and their research potential than on their track record and number of publications.

**Environment:** there should be some evidence of institutional commitment in terms of space and time to perform the research.

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Last updated on 20th December, 2001

# Center for Scientific Review

## National Institutes of Health

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## CSR SCORING PROCEDURES

### NUMERICAL RATING

Each scored grant application is assigned a single, global score that reflects the overall impact that the project could have on the field based on consideration of the five review criteria (significance, approach, innovation, investigator, and environment), with the emphasis on each criterion varying from one application to another, depending on the nature of the application and its relative strengths. The best possible priority score is 100 and the worst is 500. Individual reviewers mark scores to two significant figures, e.g., 2.2, and the individual scores are averaged and then multiplied by 100 to yield a single overall score for each scored application, e.g., 253. Abstaining members and those not present during the discussion do not assign a numerical rating and are not counted in calculating the average of the individual ratings. For research applications, reviewers are also asked to recommend that half the applications not be scored and to spread final scores to achieve a median score of 300. (Any member of the scientific review group may request that an application be scored, in which case all members must score the application.) To the extent that the study section does not score some applications, the scoring range is altered. If half of the applications are not scored, then the remaining applications should be scored from 100-300. If only 25% of the applications are not scored then the remaining applications should be scored from 100-400. Note that these procedures for scoring only half of the research applications do not apply to fellowships and career applications; all fellowships and career applications are scored.

### PERCENTILE CONVERSION

Research grant applications (R01s) reviewed in CSR study sections are assigned a percentile rank. The conversion of priority scores to percentile rankings is based on scores assigned to applications reviewed during the current plus past two review rounds. Applications reviewed by a standing study section are percentiled against all applications reviewed by that same study section for the three consecutive rounds. Applications reviewed by Special Emphasis Panels (SEPs) are percentiled against the parent study section database if at least 30% of the reviewers are current or recent (during the last 2 years) regular members of that study section. Applications reviewed by SEPs where fewer than 30% of the reviewers are current or recent members of a standing study section are given a percentile based on the distribution of scores assigned by all CSR study sections. Note that at CSR, applications other than R01s (e.g., fellowships, small business applications) are not percentiled.

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Last updated on 8th September, 2003

# Center for Scientific Review

## National Institutes of Health

### Referral & Review

## REVIEW PROCEDURES FOR SCIENTIFIC REVIEW GROUP MEETINGS

### REVIEW PROCEDURES

The guiding principles for the initial review of research project grant applications are based on the Public Health Service (PHS) Scientific Peer Review Regulations that state that peer review groups are to make recommendations concerning the scientific merit of applications. The specific criteria used to assess the merit of research project grant applications will vary with types of applications reviewed, such as Investigator Initiated Research Project Grants ([R01](#)), Academic Research Enhancement Awards ([R15](#)), the National Research Service Awards ([F32](#), [F33](#), etc.), Small Business Innovation Research Grants, etc.

For the review of investigator-initiated research grant applications (e.g., [R01](#) and [R15](#)), a streamlined procedure will be employed to determine whether the applications assigned to a study section are in the upper or lower half. This procedure is described in the document [CSR Streamlined Review Procedures](#). Prior to the meeting of the study section, reviewers will be asked to identify applications that they feel are not in the upper half and will consequently not be discussed at the study section meeting. If two reviewers/discussants agree that an application is not in the upper half, it will be designated as such, and a list prepared by the SRA identifying proposed applications not in the upper half will then be sent to reviewers a few days prior to the study section meeting. After seeing this list any review group member not in conflict may disagree and identify an application that he/she believes is in the upper half and, therefore, should receive full discussion. At the beginning of the meeting, the list will be read aloud for final concurrence by the entire study section. If any member of the review group not in conflict questions the rating or wishes to comment on the application, it will be discussed and considered by the entire review group in the normal sequence of review.

The Chairperson of the scientific review group introduces each application designated for discussion and calls upon the individuals assigned by the SRA to present their evaluations. The assigned discussants are then called upon for their comments and group discussion follows. If prior to substantial discussion the scientific review group determines that the application being discussed should actually not be placed in the upper half, it may recommend that the application not be scored. Such a designation requires unanimous agreement of the scientific review group. Otherwise, after sufficient discussion has ensued, the Chairperson calls for a priority rating to be

assigned to the application. Ratings will be assigned by regularly appointed members of the scientific review group and by those serving as temporary members. Reviewers are encouraged not to abstain. However, a reviewer who feels unable to assess the merit of an application, as evidenced by his/her prior discussion or recommendation for deferral, should mark the vote sheet "AB".

In addition, if there are comments or serious concerns regarding the use of human subjects or animal welfare or biohazards, a motion may be initiated that the application should be coded to reflect these comments or concerns, and an appropriate note will be included in the summary statement.

If additional information is needed before a review group can make a recommendation, a motion for **deferral** may be entertained. The review group may, by majority vote, defer an application for additional information or, if information necessary to evaluate the application can be obtained only by visual inspection of the facilities, for a project site visit. Any member may nominate an application for deferral.

## **NUMERICAL RATING**

Each scored application is assigned a single, global score that reflects the overall impact that the project could have on the field based on consideration of the five review criteria (significance, approach, innovation, investigator, and environment), with the emphasis on each criterion varying from one application to another, depending on the nature of the application and its relative strengths. The best possible priority score is 100 and the worst is 500. Individual reviewers mark scores to two significant figures, e.g., 2.2, and the individual scores are averaged and then multiplied by 100 to yield a single overall score for each scored application, e.g., 253. Abstaining members and those not present during the discussion do not assign a numerical rating and are not counted in calculating the average of the individual ratings. Reviewers are asked to recommend that half the applications not be scored and to spread final scores to achieve a median score of 300. (Any member of the scientific review group may request that an application be scored, in which case all members must score the application.) To the extent that the study section does not score some applications, the scoring range is altered. If half of the applications are not scored, then the remaining applications should be scored from 100-300. If only 25% of the applications are not scored then the remaining applications should be scored from 100-400.

## **BUDGET**

The budget recommendation should be based upon the appropriateness of direct costs for the proposed research for each year of support requested. Attention should be given to the need for all personnel listed in the application and their percent effort in relation to the scope of works. Reviewers should keep in mind the applicant's ability to move funds amongst budget categories, therefore, the appropriateness of the total budget and the requested duration of support in relation to the research proposed should be emphasized.

Reviewers may identify areas of potential overlap with other supported research. However, potential overlap may be neither a reason for altering the budget nor may it affect the priority score.

Information regarding potential overlap is included in the Scientific Review Administrator's note at the end of the summary statement.

## FOREIGN ORGANIZATIONS

In addition to the regular review criteria, foreign applications are evaluated in terms of special opportunities for furthering research programs through the use of special talents, resources (human subjects, animals, diseases, equipment or technologies), populations or environmental conditions in the applicant country which are not readily available in the United States or which provide augmentation of existing United States resources. In addition, it should be noted whether similar research is being done in the United States and whether there is a need for additional research in the area of the proposal. These special review criteria are not applied to applications from domestic institutions that include a significant foreign component.

## RESEARCH INVOLVING HUMAN SUBJECTS

Applicant organizations have the primary responsibility for safeguarding the rights and welfare of individuals who participate as subjects in research activities supported by the NIH. However, the NIH also relies on its scientific review groups and National Advisory Councils or Boards to evaluate all applications and proposals involving human subjects for compliance with the Department of Health and Human Services human subject regulations.

There are several considerations for review of applications involving human subjects. These can be clustered into two broad areas: Protection of subjects from research risks; and the inclusiveness of the study population. Protection issues include questions regarding safety and welfare of the subjects, including data and safety monitoring where applicable. Inclusion issues reflect the appropriate involvement of women, minorities and children

Assessment of scientific and technical merit of applications involving human subjects must include an evaluation of the proposed composition of the study population and its appropriateness for the scientific objectives of the study. If representation of women, minorities, or children in the study design is inadequate to answer the scientific question(s) addressed and justification for the selected study population is inadequate, reviewers should consider this to be a scientific weakness or deficiency in the study design and must consider this weakness in assigning a priority score.

More detailed instructions for reviewing grant applications involving human subjects, and exemptions, are available at the following URL: [http://grants.nih.gov/grants/peer/hs\\_review\\_inst.pdf](http://grants.nih.gov/grants/peer/hs_review_inst.pdf)

### Definitions:

When considering applications that involve human subjects it is important for reviewers to keep a number of definitions of terms in mind:

**Human subjects:** Federal regulations define "human subject" as a "living individual about whom an investigator obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." The regulations extend to the use of human organs, tissue and

body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects. A subset of research involving human subjects may qualify for exemption, but justification must be provided under the heading "Protection of Human Subjects from Research Risk". The use of autopsy materials is governed by applicable state and local law and is not directly regulated by the Federal human subject regulations.

**Clinical research** is defined as: (1) Patient-oriented research, i.e., research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. (Excluded from the definition of patient-oriented research are in vitro studies that utilize human tissues that cannot be linked to a living individual.) Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; (2) Epidemiologic and behavioral studies; or (3) Outcomes research and health services research. <http://www.nih.gov/news/crp/97report/execsum.htm>

**A Clinical Trial** is operationally defined as a prospective biomedical or behavioral study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions.

**An NIH-defined Phase III clinical trial** is a broadly based prospective clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

A **valid analysis** is required in phase III clinical trials. This means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis are:

- Allocation of study participants of both sexes/genders and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,
- Unbiased evaluation of the outcome(s) of study participants, and
- Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

**Research Conducted in a Foreign Country:** For foreign awards, and domestic awards with a foreign component, the NIH policy on inclusion of women and minority groups in research is the same as that for research conducted in the U.S. If there is scientific rationale for examining subpopulation group differences within the foreign population, investigators should consider designing their studies to accommodate these differences.

**Children:** For purposes of this policy, a child is an individual under the age of 21 years. This

definition does not affect the human subject protection regulations for research on children (45 CFR 46) and their provisions for assent, permission, and consent, which remain unchanged. State laws define what constitutes a "child," for the purpose of determining whether or not a person can legally consent to participate in a research study.

## EXEMPTION FROM HUMAN SUBJECTS REGULATIONS

If the applicant designates an exemption from the human subjects regulations, reviewers should evaluate the information provided to determine if the designated exemption is appropriate. With regard to exemption 4, although reviewers need not evaluate questions related to research risks or the inclusion of women and minorities, the appropriate inclusion of children **DOES** need to be addressed for these applications.

## PROTECTION OF HUMAN SUBJECTS

If the proposed research involves human subjects, and does not qualify as being exempt, it is considered clinical research (see definition above) and reviewers must evaluate the plan to protect human subjects. The applicant's research plan should include four elements under the heading "Protection of Human Subjects from Research Risk". Reviewers are asked to evaluate each of the four elements:

- **Risks to the subjects:** discussion of human subject involvement and characteristics, source of material, and potential risks. This includes discussion of the likelihood and seriousness of potential risk to subjects including, if applicable, risks to special populations. Where appropriate, alternate treatments and procedures, including risks and benefits should be considered. If a test article (Investigational New Drug, device, or biologic) is involved, or if the applicant proposes using a drug or device in a method that may not have FDA approval, the test article must be named and the status with regard to FDA submission/approval must be stated.
- **Adequacy of protection against risks:** discussion of plans to protect against or minimize potential risks and assessment of their likely effectiveness. Where appropriate, this section should include discussion of plans for ensuring necessary medical or professional intervention in the case of adverse effects. Also included are recruitment plans and description of the process for obtaining informed consent, including the information to be provided to subjects.
- **Potential benefit of the proposed research to the subjects and others:** discussion of why the anticipated risks are reasonable in relation to the anticipated benefits to the subjects and to others.
- **Importance of the knowledge to be gained:** discussion of why the risks to subjects are reasonable in relation to the importance of the knowledge to be gained.

There is a fifth level of protection involving data and safety monitoring, if a clinical trial is proposed. All applications proposing clinical trials research (see definition above) should include plans for Data and Safety Monitoring that describe the entity to be responsible for the monitoring as well as the policies and procedures for adverse event reporting. An NIH defined Phase III clinical trial (see definition above) also requires establishment of a Data and Safety Monitoring Board to provide this oversight. Reviewers should look for this information within the applicants Protection of Human

Subjects section and evaluate it accordingly.

Based on the evaluation of whether the applicant has adequately addressed Human Subjects Protection according to these criteria and subsequent discussion, the study section may score the application with no concerns or with comments or concerns that may affect the score to a level commensurate with the seriousness of the concern. A "concern" is a scientific review group finding regarding human subjects that requires resolution by program staff prior to award; a "comment" is a scientific review group observation that will be communicated in the summary statement as a suggestion to the principal investigator. No awards will be made until all expressed concerns about human subjects have been resolved to the satisfaction of the NIH.

## **Inclusion of Women and Minorities as Subjects in Clinical Research**

It is the policy of NIH that women and members of minority groups and their subpopulations **must** be included in all NIH-funded clinical research (see definition above), unless a clear and compelling rationale and justification establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Cost is not an acceptable reason for exclusion, except when the study would duplicate data from other sources. Women of childbearing potential should **not** be routinely excluded from participation in clinical research. The inclusion of women and members of minority groups, and their subpopulations, must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. The objective should be to actively recruit and retain the most diverse study population consistent with the purposes of the research project.

When an NIH-defined Phase-III clinical trial (see definitions above) is proposed, the Research Plan must include a description of plans to conduct valid analysis (see definition above) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable.

Accordingly, reviewers should consider these inclusion criteria in their evaluations and:

- Evaluate the proposed plan for the inclusion of minorities and both genders for appropriate representation or evaluate the proposed justification when representation is limited or absent (e.g., inclusion is inappropriate with respect to the health of the subjects, or the purpose of the research),
- Determine whether the design of clinical trials is adequate to measure differences when warranted,
- Evaluate the plans for analysis (for NIH-defined Phase III clinical trials),
- Evaluate the plans for recruitment/outreach for study participants, and
- Include these evaluations as part of the scientific assessment and priority score.

Additional information concerning the NIH Policy on Inclusion of Women and Minorities as Subjects in Clinical Research is available at:[http://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm).

## Inclusion of Children as Participants in Research

It is the policy of NIH that children (i.e., individuals under the age of 21) **must** be included in all human subjects research supported by the NIH, not solely clinical research as is the case for women and minorities, unless there are scientific or ethical reasons not to include them. This policy applies to all research involving human subjects, **including** research that is otherwise "exempt." Proposals for research involving human subjects **must** include a description of plans for including children. If children will be excluded from the research, the application must present an acceptable justification for the exclusion.

The section in the application titled "Inclusion of Children" should provide either a description of the plans to include children and a rationale for selecting or excluding a specific age range of child, or an explanation of the reason(s) for excluding children as participants in the research. When children are included, the plan **must** also include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.

Reviewers should assess each application as being "acceptable" or "unacceptable" in regard to the age-appropriate inclusion or exclusion of children in the proposed research project. Specific exclusionary circumstances and other pertinent information on the inclusion of children in NIH-supported research may be found at: <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

## RESEARCH INVOLVING VERTEBRATE ANIMALS

Although the recipient institution and investigator bear the major responsibility for the proper care and use of animals, NIH staff, scientific review groups, and Councils and Boards share this responsibility. Care and use of vertebrate animals in research must conform to applicable law and Public Health Service policy, especially the **Principles for Use of Animals**. These principles can be summarized as two broad rules:

- The project should be worthwhile and justified on the basis of anticipated results for the good of society and the contribution to knowledge, and the work should be planned and performed by qualified scientists;
- Animals should be confined, restrained, transported, cared for, and used in experimental procedures in a manner to avoid any unnecessary discomfort, pain, or injury. Special attention must be provided when the proposed research involves dogs, cats, nonhuman primates, large numbers of animals, or animals that are in short supply or are costly.

The evaluation by scientific review group members is to take into consideration the investigator's response to the following five points:

1. Provide a detailed description of the proposed use of the animals in the work previously outlined in the experimental design and methods section. Identify the species, strains, ages, sex and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers used. If animals are in

short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and their numbers.

3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices where appropriate to minimize discomfort, distress, pain, and injury.
5. Describe any euthanasia method to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Research using nonhuman primates or chimpanzees requires special attention by Review and Institute staff, so their use must be identified during review and in the vertebrate animal section of the summary statement. There are two situations using animal tissue that do not invoke application of PHS Policy on Vertebrate Animal Use. These are 1) use of blood obtained by a veterinarian in normal medical practice and given to an investigator after testing; and 2) use of left over tissue, as from a slaughterhouse. In both cases, there has been no "custom" request and thus no live vertebrate animals are involved.

Any comments or concerns that scientific review group members may wish to express regarding the appropriateness of the choice of species and numbers involved, the justification for their use, and the care and maintenance of vertebrate animals used in the project will be discussed in a special note (**ANIMAL WELFARE**) in the summary statement. A "concern" is a scientific review group finding regarding animal care or use that requires resolution by program staff prior to award; a "comment" is a scientific review group observation that will be communicated in the summary statement as a suggestion to the principal investigator. Questions may be directed to the Office for Protection from Research Risks. No award will be made unless the applicant institution has given the NIH Office for Protection from Research Risks an acceptable assurance of compliance with the PHS policy and all concerns or questions raised by the scientific review group have been resolved to the satisfaction of the NIH. If concerns are expressed regarding the proper use and care of animals, a recommendation may be made that no further consideration be given to the application. This can be done by either appropriate language in the summary statement (applications eligible for streamlined review) or by majority vote (applications not eligible for streamlined review).

## BIOHAZARDS

The investigator and the sponsoring institution are responsible for protecting the environment and research personnel from hazardous conditions. As with research involving human subjects, reviewers are expected to apply the collective standards of the professions represented within the scientific review group in identifying potential hazards, such as inappropriate handling of oncogenic viruses, chemical carcinogens, infectious agents, radioactive or explosive materials, or recombinant DNA.

If applications pose special hazards, these hazards will be identified and any concerns about the adequacy of safety procedures highlighted as a special note (**BIOHAZARD**) on the summary statement. No award will be made until all concerns about hazardous procedures or conditions have

been resolved to the satisfaction of the NIH.

## AVOIDING CONFLICTS OF INTERESTS DURING SCIENTIFIC REVIEW GROUP MEETINGS

At the beginning of each meeting, the Scientific Review Administrator orients the members by explaining the NIH conflict-of-interest policy. A member must leave the room when an application submitted by his/her own organization is being discussed or when the member, his/her immediate family, or close professional associate(s) has a financial or vested interest even if no significant involvement is apparent in the proposal being considered. If the member is available at the principal investigator's institution for discussions; is a provider of services, cell lines, reagents, or other materials, or writer of a letter of reference, the member must be absent from the room during the review. Members are also urged to avoid any actions that might give the **appearance** that a conflict of interest exists, even though he or she believes there may not be an **actual** conflict of interest. Thus, for example, a member should not participate in the deliberations and actions on any application from a recent student, a recent teacher, or a close personal friend. Judgment must be applied on the basis of recency, frequency, and strength of the working relationship between the member and the principal investigator as reflected, for example, in publications. Other examples are a project that closely duplicates work ongoing in the member's laboratory, or an application from a scientist with whom the member has had longstanding differences that could reasonably be viewed as affecting the member's objectivity.

If an application is submitted naming a participating individual from another institution, that individual is not considered to have a relationship with the applicant institution that constitutes a conflict of interest. Consequently, (1) that named individual may review other applications from the applicant institution; and (2) other individuals from the institution of the named individual may be used as reviewers for the submitted application, **so long as any real or apparent conflict of interest is resolved**. The SRA will document that there is no conflict of interest.

For peer review consultants who are not federal employees, all separate organizational components/schools of multi-component academic institutions, hospitals, health centers, and research institutes may be considered to be sufficiently independent such that an employee of one component can review an application from another component without a conflict of interest, so long as any other real or apparent conflict of interest is resolved. In practice, for example, this means that:

1. the separate campuses of the California State system are considered separate components in the same way that the separate campuses of the University of California system are so noted in the Federal Register citation above;
2. the separate campuses of the Harvard system are considered separate components;
3. the Johns Hopkins Bayview Medical Center and the School of Arts and Sciences, Homewood Campus, are separate components;
4. the Johns Hopkins Schools of Arts and Sciences and of Engineering, Homewood Campus, are separate components;

however,

5. for purposes of this blanket waiver, the Departments of Biology and Chemistry within the

School of Arts and Sciences are NOT separate components.

In addition, ***so long as any real or apparent conflict of interest is resolved:***

If an individual supplies a resource or service to an applicant, and that resource or service is freely available to anyone in the scientific community, neither the institution nor the individual supplying the resource is in conflict.

For fellowship and K award applications, peer reviewers who write reference letters for an applicant are in conflict and must leave the room for the review of the application; this does not, however, constitute an ***institutional*** conflict. If the applicant's sponsor is a member of the SRG, this constitutes a ***member*** conflict for the study section (i.e., the study section may not review the application).

For conference grant applications, the originators, planning group members, and proposed speakers are in conflict, but their institutions are not, and this situation does not generate a study section conflict.

Reviewers from institutions that are part of a multi-center network (e.g., accrual sites for a multi-center clinical trial) are not in conflict with other applications/proposals from other institutions in the network; furthermore, reviewers from institutions that provide members of an applicant's Advisory Board or Data and Safety Monitoring Board are not in conflict with other applications/ proposals from those institutions.

A reviewer must leave the room during discussion of an application if he/she is a member of, or has a financial interest in a for-profit organization submitting the application. This includes ownership of stock in, or being a consultant for a for-profit organization. A reviewer should also leave the room during discussion of an application if being present would give the ***appearance*** of a conflict of interest. Examples would be, an application from a for-profit organization that provides substantial financial funding to the reviewer's organization or laboratory.

Prior to the scientific review group meeting, each reviewer will receive a certificate of Conflict of Interest and Confidentiality and a list of applications that will be reviewed. Reviewers must notify the Scientific Review Administrator of any conflict of interest prior to the meeting and certify that the confidentiality of the review procedures will be maintained.

At the end of the scientific review group meeting, the SRA will obtain written certification from all members that they have not participated in any reviews of applications when their presence would have constituted a real or apparent conflict of interest and that the confidentiality of actions will be maintained. In addition, each study section keeps a log, prepared by the Grants Assistant and maintained in the study section office, of which members left the room because of potential conflict of interest and for which applications.

## **CONFIDENTIALITY AND COMMUNICATIONS WITH INVESTIGATORS**

All materials pertinent to the applications being reviewed are privileged communications prepared

for use only by consultants and NIH staff, and should not be shown to or discussed with other individuals. Review group members must not independently solicit opinions or reviews on particular applications or parts thereof from experts outside the pertinent initial review group. Members may, however, suggest scientists from whom the SRA may subsequently obtain advice. Consultants are required to leave all review materials with the SRA at the conclusion of the review meeting. Privileged information in grant applications shall not be used to the benefit of the reviewer or shared with anyone.

Under no circumstances shall consultants advise investigators, their organizations, or anyone else of recommendations or discuss the review proceedings. The investigator may be led into unwise actions on the basis of premature or erroneous information. Such advice also represents an unfair intrusion into the privileged nature of the proceedings and invades the privacy of fellow consultants serving on review committees and site visit teams. A breach of confidentiality could deter qualified consultants from serving on review committees and inhibit those who do serve from engaging in free and full discussion of recommendations.

Except during site visits, there must be no direct communications between consultants and investigators. Consultants' requests for additional information and telephone inquiries or correspondence from investigators must be directed to the SRA, who will handle all such communications.

## **SCIENTIFIC MISCONDUCT**

"Misconduct" or "misconduct in science" is defined at 42 CFR 50.102 as fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting or reporting research. It does not include honest error or honest differences in interpretation or judgments of data.

Review of grant/cooperative agreement applications and contract proposals for scientific merit will ordinarily not be delayed by pending or ongoing inquiry or investigation. To avoid influencing the review process, HHS awarding units will not inform members of scientific review groups about instances of possible misconduct or the status of ongoing investigations. However, if certain instances have received such extensive publicity that the review may be compromised, the CSR Research Integrity Officer (RIO) will discuss the matter with the Agency Research Integrity Liaison Officer (ARILO). Findings from completed investigations should be shared with scientific review group when an accurate disclosure of the facts in the case is necessary for an objective and thorough review.

The scientific review group should not review an application about which an allegation of misconduct has surfaced from one of its members. The SRA should report the allegation to the CSR RIO. The RIO will involve appropriate CSR staff and the ARILO in determining the manner in which the allegation will be treated

In all cases of suspected misconduct, it is essential that the SRA stress to the reviewers the seriousness of such allegations and the potential harm that may result if confidentiality is not strictly maintained. In addition, it is important for the SRA to assure the reviewers that the suspicions

identified will be taken seriously and pursued by the HHS. In no instance shall the SRA or a reviewer communicate the scientific review group's concerns to the principal investigator or applicant institution.

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