

RESEARCH ON CRYSTAL DEPOSITION ARTHROPATHIES

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Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATION:

National Institutes of Health (NIH)

(<http://www.nih.gov>)

COMPONENTS OF PARTICIPATING ORGANIZATION:

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

(<http://www.nih.gov/niams/>)

National Institute on Aging (NIA)

(<http://www.nih.gov/nia/>)

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER: 93.846 (NIAMS)
and 93.866 (NIA)

LETTER OF INTENT RECEIPT DATE: July 19, 2004

APPLICATION RECEIPT DATE: August 19, 2004

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PURPOSE OF THIS RFA

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute on Aging (NIA) invite applications for research on improved

diagnosis and treatment of the major crystal deposition arthropathies including gout, calcium pyrophosphate dihydrate (CPPD) crystal deposition disease and hydroxyapatite crystal deposition disease (also known as basic calcium phosphate crystallopathy). The applications may be for individual research projects (R01) or for exploratory/developmental grants (R21). The crystal deposition arthropathies constitute significant public health problems. These problems are anticipated to grow in scope in view of the increased number of elderly in our population, and the increasing numbers of people with osteoarthritis predisposing cartilage to calcification disorders. The Request for Applications (RFA) is based, in part, on the scientific opportunities identified in the NIAMS Roundtable held in 2003: "Opportunities for Translational Research on Articular Crystal Deposition Diseases: Gout, CPPD Crystal Deposition Disease, Hydroxyapatite Deposition Arthropathy."

RESEARCH OBJECTIVES

Gout is caused by the deposition of uric acid (monosodium urate) crystals in connective tissue and in the joint space. Clinical manifestations include bouts of gouty arthritis, tophaceous deposits, uric acid and calcium oxalate kidney stones, and, rarely, interstitial nephropathy. In some cases, uric acid crystals in the joints trigger severe destruction of articular cartilage, leading to pain and disability.

Uric acid is the normal end product of purine metabolism in humans. It is generated as a result of nucleotide turnover and breakdown of dietary purines, and its elimination is controlled primarily by the kidneys. Because the human uric acid oxidase (uricase) gene contains a mutation that renders it transcriptionally silent, normal serum levels of uric acid are very close to the level at which urate becomes insoluble in vitro, rendering urate balance precarious. Although elevated serum uric acid levels are the first sign of gout, only about 20% of people with hyperuricemia develop the disease.

Gout affects approximately 1% of the U.S. population, and remains a significant public health concern. The prevalence of gout is much higher in certain ethnic groups, including Asian Pacific Islanders, Filipinos, Maoris, and Samoans. Gout prevalence is also reportedly rising in African Americans. Although gout primarily affects men, disease prevalence is increasing among elderly women along with increased longevity, and may be linked to the common use of diuretics and chronic renal insufficiency in this population. Reduced estrogen levels in postmenopausal women may also play a role, as estrogen is a uricosuric agent.

Refractory gout still exists, and the numbers of affected patients may, in fact, be increasing. This could be due to the limited scope of currently available urate-lowering drugs and the relatively common and potentially life-threatening toxicity of the most

versatile uric acid–lowering drug, allopurinol, which blocks urate production by inhibiting xanthine oxidase. Another contributing factor is the increasing number of people receiving kidney and heart transplants and the use of cyclosporine to prevent tissue rejection in these patients. More than 10% of transplant patients develop gout within 3 years of treatment with cyclosporine, and the rapidly expanding tophi and severe attacks of gouty arthritis that occur in these patients are often refractory to therapy.

The development of new treatments for gout has not kept pace with medical needs. An estimated 10–20% of gout cases in the U.S. are refractory to treatment because patients either cannot take allopurinol or are resistant to the drug. In addition, the effectiveness of uricosuric drugs such as probenecid is limited by various factors. The principal therapies for acute gout attacks, i.e., nonsteroidal anti-inflammatory drugs (including COX-2 inhibitors), glucocorticoids, and colchicine, also have limitations and cannot prevent the progressive crystal-induced connective tissue destruction that occurs in some gout patients.

Non-urate calcium-containing crystal deposition diseases that affect the joints and surrounding structures include calcium pyrophosphate dihydrate (CPPD) crystal deposition disease and hydroxyapatite crystal deposition disease (also known as basic calcium phosphate crystallopathy). Some individuals have a mixture of CPPD and hydroxyapatite crystals in affected joints. The prevalence and incidence of calcium crystal arthropathies are expected to increase as a result of the growing elderly population in the U.S. and increasing numbers of people with osteoarthritis predisposing cartilage to calcification disorders.

Manifestations of CPPD disease may include intermittent attacks of pseudogout (acute inflammatory arthritis), chronic degenerative arthropathy, and calcification of articular cartilage. CPPD disease can occur idiopathically, and in rare cases as a hereditary condition. Crystal deposition may be associated with a variety of metabolic disorders and can also occur as a result of trauma, injury or surgery.

The basic calcium phosphate arthropathies include calcific periartthritis syndromes that can occur as primary or secondary disease manifestations and may occur in a familial fashion, in calcific tendonitis and bursitis, intraarticular arthropathies such as Milwaukee shoulder syndrome, and periartthropathies. Tumoral calcinosis syndrome is a rare form of basic calcium phosphate marked by large, periarticular tophaceous deposits containing hydroxyapatite and other basic calcium phosphate crystals.

CPPD or hydroxyapatite crystals are present in synovial fluid extracted from the joints of 30-60% of people with osteoarthritis, however, a distinct pattern of joint involvement

distinguishes CPPD and hydroxyapatite deposition diseases from "garden variety" osteoarthritis. Definitive diagnosis of the calcium crystal deposition arthropathies is made by identifying specific crystal types in synovial fluid samples, which can be technically difficult. Chondrocalcinosis and other soft tissue calcification may also be visible on X rays of joints in some patients, although these patients may be asymptomatic.

CPPD and hydroxyapatite crystals may also contribute directly or indirectly to osteoarthritis (OA). However, the mechanisms involved are still unclear, and there is controversy as to whether crystals can actually cause OA in some cases rather than just exacerbating the disease.

In addition to studies of possible direct and indirect effects of crystals on OA, ongoing research on calcium crystal arthropathies includes studies of factors involved in cartilage mineralization, investigations using animal models of articular calcification, and genetic studies of familial disorders of calcium crystal deposition. Recent advances include the identification of two molecules that play a key role in some forms of CPPD and hydroxyapatite deposition diseases:

the pyrophosphate-generating ectoenzyme PC-1 (a nucleoside triphosphate pyrophosphohydrolase) and ANKH, a multiple-pass transmembrane protein expressed in articular cartilage and other tissues that is a putative pyrophosphate transporter. Inorganic pyrophosphate is both a potent inhibitor of hydroxyapatite deposition and an essential component of CPPD crystals, indicating that it plays a central role in calcium crystal deposition diseases.

This RFA is intended to stimulate research aimed at elucidating the pathogenesis of these disorders and engender the development of improved methods of diagnosis and treatment. Topics of interest include but are not limited to:

Gout:

- o Improving understanding of the fundamental pathobiology of gout, including formation of tophi and the relationship between crystals and pathology in arthritis
- o Addressing the problem of treatment failure
- o Determining why uric acid crystal deposition occurs in only some people with hyperuricemia, with the goal of developing approaches that prevent crystal formation in susceptible individuals
- o Developing new methods for early diagnosis
- o Conducting small-scale epidemiologic studies on gout
- o Studying the genetic basis of drug responsiveness and drug resistance
- o Developing new therapeutic agents
- o Developing new animal models

Calcium Crystal Arthropathies:

- o Improving understanding of the relationship between calcium crystals and pathology
- o Improving understanding of the basic biology of the link between aging tissue changes and development of calcium crystal deposition diseases
- o Clarifying the relationship between calcium crystal deposition and osteoarthritis
- o Determining why some people with OA develop CPPD crystals in their joints, some develop hydroxyapatite crystals, and some develop both
- o Developing methods for early diagnosis of disease using biomarkers and imaging modalities
- o Identifying of risk factors for disease
- o Developing new treatments, including ways to alleviate problems in patients who already have crystal deposits as well as ways to prevent crystal formation in specific joints, such as the knee, hip, shoulder, temporomandibular joint, etc.
- o Developing new animal models

Please note that large-scale clinical and epidemiologic studies are beyond the scope of this RFA.

MECHANISMS OF SUPPORT

This RFA will use the NIH R01 (investigator-initiated research project grant) and the R21 (exploratory/developmental research grant) award mechanisms. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is June 1, 2005. Applications that are not funded in the competition described in this RFA may be resubmitted as NEW investigator-initiated applications using the standard receipt dates for NEW applications described in the instructions to the PHS 398 application.

R01 Applications. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will vary also. This RFA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (see <http://grants.nih.gov/grants/funding/modular/modular.htm>).

Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

R21 Applications. This mechanism is to be used by investigators experienced in arthritis and musculoskeletal diseases research who wish to conduct innovative, high-risk studies. Also encouraged to apply are investigators with expertise in fields other than arthritis and musculoskeletal diseases that wish to establish new research programs on these diseases.

Exploratory/developmental studies are not intended for large-scale undertakings or to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach which may not be justifiable through existing research to compete as a standard research project grant (e.g., R01), and to develop a research basis for a subsequent application through other mechanisms, i.e., R01, P01.

Exploratory/developmental (R21) grants may not exceed \$100,000 per year in direct costs. The total project period for an R21 application submitted in response to this RFA may not exceed two years. These grants are non-renewable and continuation of projects developed under the R21 program will be through the traditional unsolicited (R01 or P01) grant programs.

This RFA uses just-in-time concepts. It also used the modular budgeting as well as the non-modular budgeting formats (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less, use the modular budget format. Otherwise follow the instructions for non-modular budget research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps2001/part_i_1.htm.

Investigators proposing to conduct small, pilot/toxicity clinical trials are advised to review the NIAMS guidelines for preparation of clinical trial applications and the NIAMS guidelines for Data and Safety Monitoring Boards (<http://www.nih.gov/niams.htm>).

FUNDS AVAILABLE

The estimated funds available for the first year of support for the program are \$1,200,000 in FY 2005 to fund 3 to 5 new grants in response to this RFA. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the NIAMS provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. At this time, it is not known if this RFA will be reissued.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- o For-profit or non-profit organizations
- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the Federal government
- o Domestic or foreign institutions/organizations
- o Faith-based or community-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

- o Direct your questions about scientific/research issues to:

Bernadette Tyree, Ph.D.
Director, Cartilage and Connective Tissue Program
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20892-4872
Telephone: (301) 594-5032
FAX: (301) 480-1284
Email: tyreeb@mail.nih.gov

Jill L. Carrington, Ph.D.
Director, Musculoskeletal Biology
Biology of Aging Program
National Institute on Aging
7201 Wisconsin Avenue, Suite 2C231
Bethesda, MD 20892

Telephone: (301) 496-6402
FAX: (301) 402-0010
Email: Carringtonj@nia.nih.gov

o Direct your questions about peer review issues to:

Teresa Nesbitt, D.V.M., Ph.D.
Chief, Review Branch
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20892-4872
Telephone: (301) 594-4953
FAX: (301) 480-4543
Email: nesbitt@mail.nih.gov

o Direct your questions about financial or grants management matters to:

Michael Morse
Grants Management Branch
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20892-4872
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: morsem@mail.nih.gov

Linda Whipp
Grants and Contracts Management Office
National Institute on Aging
7201 Wisconsin Avenue, Suite 2N212, MSC 9205
Bethesda, MD 20892
Telephone: (301) 496-1472
FAX: (301) 402-1758
Email: whipl@nih.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

- o Descriptive title of the proposed research
- o Name, address, and telephone number of the Principal Investigator
- o Names of other key personnel
- o Participating institutions

o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIAMS staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Teresa Nesbitt, D.V.M., Ph.D.
Chief, Review Branch
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20892-4872
Telephone: (301) 594-4953
FAX: (301) 480-4543
Email: nesbitt@mail.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dunandbradstreet.com/>. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS

RESEARCH PLAN – The research plan (a-d) is limited to 25 pages for R01 applications and 10 pages for R21 applications. Applications that exceed the page limit will be returned without review. An appendix may be included in the application; however, the appendix is not to be used to circumvent the page limit of the research plan.

For the R21 application, preliminary data supporting feasibility of approach are not required, however, if included, the section may not exceed 1 page. In addition, a

paragraph should be included in the Significance section of the application that specifies either how the project presents a new direction for the work performed in the PI's laboratory or the innovative nature of the research question or approach, and how it may advance understanding of the crystal deposition arthropathies.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS:

Applications requesting up to \$250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in \$25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: <http://grants.nih.gov/grants/funding/phs398/labels.pdf>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must be sent to:

Teresa Nesbitt, D.V.M., Ph.D.
Chief, Review Branch
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20892-4872
Telephone: (301) 594-4953
FAX: (301) 480-4543
Email: nesbitt@mail.nih.gov

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfounded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIAMS and the NIA. Incomplete applications will not be reviewed.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- o Undergo 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 and assigned a priority score
- o Receive a written critique
- o Receive a second level review by an appropriate national advisory council or board.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The

scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

- o Significance
- o Approach
- o Innovation
- o Investigator
- o Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. 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.

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?

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?

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)?

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?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, all R21 applications will also be reviewed with respect to the following:

o In the context of this RFA, the R21 exploratory/developmental grants are to be used to either: a) gather preliminary data to develop a research basis for a subsequent application through other mechanisms, i.e., R01, P01 or b) explore the feasibility of an innovative or conceptually creative research question or approach that may not be justifiable through existing research to compete as a standard research project grant (e.g., R01).

o Preliminary data supporting feasibility of approach are not required.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: July 19, 2004
Application Receipt Date: August 19, 2004
Peer Review Date: TBA
Council Review: May, 2005
Earliest Anticipated Start Date: June 1, 2005

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o Scientific merit (as determined by peer review)
- o Availability of funds
- o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

DATA AND SAFETY MONITORING PLAN: 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). The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998:

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

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines are available at

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at <http://grants.nih.gov/grants/funding/children/children.htm>

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov>). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at

<http://www.health.gov/healthypeople>.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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