Hispanic or Latino • Not Hispanic or Latino • American Indian/Alaskan Native • Asian • Native Hawaiian or Other Pacific Islander • Caucasian • Black or African American • Hispanic or Latino • Not Hispanic or Latino • American Indian/Alaskan Native • Asian • Native Hawaiian or Other Pacific Islander • Caucasian •Black or African American • Hispanic or Latino • Not Hispanic or Latino • American Indian/Alaskan Native • Asian

Outreach Notebook

For the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Office of the Director

Outreach Notebook for the Inclusion, Recruitment and Retention of Women and Minority Subjects in Clinical Research

Principal Investigators' Notebook

National Institutes of Health
Office of Research on Women's Health
Office of Extramural Research
NIH Outreach Notebook Committee
NIH Tracking and Inclusion Committee

How to use this Notebook

December 2002

Dear Principal Investigator:

The information in this notebook may be of assistance to you and your research team in fulfilling your responsibilities for proper conduct of clinical research under applicable federal laws and regulations, and implementation of the updated 2001 *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. This notebook serves as a complement to the updated *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*.

Outreach efforts for inclusion, recruitment and retention of research subjects necessarily span the entire clinical research spectrum, from small observational studies trials to the largest Phase III clinical trials enrolling thousands. Primary prevention studies involving apparently disease-free individuals, as well as secondary and tertiary intervention involving individuals with diagnosed diseases, are included, as are studies in which the unit of observation is on the entire community. The notebook does not mandate that participants from various populations be enrolled, nor is it a step-by-step guide through recruitment and retention. Rather, it furnishes advice on inclusion criteria, provides an overview of key elements in recruitment and retention processes, and suggests a number of practical applications, including ethical considerations. Attention to these factors in the design of a research project will assist in the appropriate inclusion of women and minorities into studies.

Specific requirements for information needed in a grant application or contract proposal will depend on particulars of the study aims, design and other factors. The reader is urged to determine these requirements by reading carefully documents included in this book and

listed in the appendices under the section "Resources Available on the Internet." This primer is an evolving document that will undergo review and revision in the future. Therefore, we welcome your comments for future editions of this book.

Sincerely,

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The committee wishes to extend its deepest appreciation to the NIH staff and those in the extramural community who contributed to the development of this notebook.

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Section 1

NIH Policies Involving the Inclusion of Women and Minorities: Review of the Inclusion Policy

REVIEW OF THE INCLUSION POLICY

I WHY, WHEN AND WHAT

A *Rationale – Why Does NIH Have the Inclusion Policy?*

The establishment and implementation of policies for the inclusion of women and minorities in clinical research funded by the National Institutes of Health (NIH) has its origins in the women's health movement. Following the issuance of the report of the Public Health Service Task Force on Women's Health in 1985, NIH established a policy in 1986 for the inclusion of women in clinical research. This policy, which *urged* the inclusion of women, was first published in the NIH Guide to Grants and Contracts in 1987. Later that year, minority and other scientists at NIH recognized the need to address the inclusion of minority populations. Therefore, in a later 1987 version of the NIH guide, a policy *encouraging* the inclusion of minorities in clinical studies was first published.

In July 1989, an *NIH Memorandum on Inclusion* stated that research solicitations should encourage inclusion of women and minorities and require a rationale if they were excluded. It also stated that executive secretaries of scientific review groups should ensure that responsiveness to this policy would be addressed and indicated in summary statements. In 1990, the Congressional Caucus for Women's Issues requested the U.S. General Accounting Office (GAO) to conduct an investigation into the implementation of the guidelines for the inclusion of women by NIH. This report, in congressional testimony, indicated that the implementation of the policy for the inclusion of women was slow and not well communicated, that gender analysis was not implemented, and that the impact of this policy could not be determined. The GAO testimony also indicated that there were differences in the implementation of the policy recommending the inclusion of minorities, and that not all institutes and centers (ICs) of NIH factored adherence to these policies into the scientific merit review (*2001 Annual Comprehensive Report: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*).

In addition to the concerns and issues raised by the advocacy community and Congress, ethical principles in conducting research with human subjects contributed to the development of the NIH inclusion policy. The ethical principle of justice highlights the importance for research to balance its burdens and benefits. In terms of the inclusion of women and minorities as research participants, this speaks to the ethical importance of ensuring that recruitment is conducted in a manner that is fair to women, men and persons from minority populations so that no group is unduly burdened and that no group is unduly benefited (McCarthy, 1994).

B *Congressional Mandate*

In order to ensure that the policies for inclusion were firmly implemented by NIH, Congress enacted these policies into Public Law through a section in the NIH Revitalization Act of 1993 (PL 103-43), entitled *Women and Minorities as Subjects in Clinical Research*. In 1994, the NIH revised its inclusion policy to meet this mandate that women and minorities *must* be included in all of its clinical research studies. PL 103-43 essentially reinforced the existing NIH policies, but with four major differences. The new law requires that:

1 NIH ensure that women and minorities and their subpopulations be included in all human subject research;

2 women and minorities and their subpopulations be included in Phase III clinical trials in numbers adequate to allow for valid analyses of differences in intervention effect;

3 cost is not allowed as an acceptable reason for excluding these groups; and,

4 NIH initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as volunteers in clinical studies.

Revised inclusion guidelines developed in response to this law were published in the *Federal Register* in March 1994, and they became effective in September 1994. The result was that NIH would not fund any grant, cooperative agreement or contract, or support any intramural project to be conducted or funded in Fiscal Year 1995 and thereafter, which did not comply with this policy. Research awards covered by this policy required the grantee to report annually on enrollment of women and men, and on the race and ethnicity of research participants.

II AMENDED INCLUSION POLICY (OCTOBER 2001)

In October 2001, NIH amended the Policy on Inclusion of Women and Minorities in Clinical Research *(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html)* to clarify the policy in regards to definitions, roles and responsibilities.

A *NIH Definition of Clinical Research*

In June 2001, NIH adopted the definition of clinical research as:

- Patient-oriented research. Research that is 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 this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies;
- Epidemiologic and behavioral studies; and
- Outcomes research and health services research.

Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

B *NIH-Defined Phase III Clinical Trials – Further Clarification*

For the purpose of the guidelines an "NIH-defined Phase III clinical trial" is a broadly based prospective Phase III 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, nonpharmacologic and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender* and race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to,

* The term gender refers to the classification of research subjects into either or both of two categories: women and men. Sex refers to biological sex, either male or female. *For inclusion purposes, biological sex should be used, either male or female.*

data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacologic studies, natural history, epidemiology and other relevant studies.

Investigators must consider the following when planning, conducting, analyzing and reporting an NIH-defined Phase III clinical trial. Based on prior studies, one of the three situations below will apply:

1 Prior Studies Support the Existence of Significant Differences

If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and relevant subpopulation comparisons, the primary question(s) to be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this.

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which depends upon the amount of information in the data set. With a very large amount of information, one could find a small but statistically significant difference that is of very little clinical importance. Conversely, with less information one could find a large difference of clinical importance that is not statistically significant.

For example, if prior research suggests that men and women respond differently to an intervention, then the Phase III clinical trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.

The research plan (for grant applications) or technical proposal (for contract solicitations) must include a description of plans to conduct analyses to detect significant differences in intervention effect by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable. The final protocol(s) approved by the Institutional Review Board (IRB) must include these plans for analysis. The award will require that for each funded protocol, investigators must report in their annual progress report cumulative subject accrual and progress in conducting analyses for sex/gender and race/ethnicity differences. If final analyses of sex/gender and race/ethnicity are not available at the time of the final progress report or competing continuation for the grant, a justification and plan ensuring completion and reporting of the analyses are required. If final analyses are required as part of the contract, these analyses must be included as part of the deliverables. These requirements will be cited in the terms and conditions of all awards for grants, cooperative agreements and contracts supporting NIH-defined Phase III clinical trials.

Inclusion of the results of sex/gender, race/ethnicity, and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

2 Prior Studies Support No Significant Differences

If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and/or relevant subpopulation comparisons, then sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

3 Prior Studies Neither Support nor Rule Out Significant Differences

If the data from prior studies neither strongly support nor strongly rule out the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and relevant subpopulation comparisons, then the NIH-defined Phase III clinical trial will be required to include sufficient and appropriate entry of sex/gender and racial/ethnic participants so that valid analysis of the intervention effects can be performed.

The term "valid analysis" 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 of the question of interest are:

- Allocation of study participants of both sexes/genders (males and females) 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.

The research plan (for grant applications) or technical proposal (for contract solicitations) must include a description of plans to conduct valid analyses by sex/gender, racial/ethnic groups and relevant subpopulations, if applicable. The final protocol(s) approved by the IRB must include these plans for analysis. The award will require that for each funded protocol, investigators must report in their

annual progress report cumulative subject accrual and progress in conducting analyses for sex/gender and race/ethnicity differences. If final analyses of sex/gender and race/ethnicity are not available at the time of the final progress report or competing continuation for the grant, a justification and plan ensuring completion and reporting of the analyses are required. If final analyses are required as part of the contract, these analyses must be included as part of the deliverables. These requirements will be cited in the terms and conditions of all awards for grants, cooperative agreements and in contracts supporting NIH-defined Phase III clinical trials.

Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

For all three situations, cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

C *New OMB Standards*

Office of Management and Budget (OMB) Directive No. 15 defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all federal reporting (including NIH). The standards were revised in 1997 and now include two ethnic categories, Hispanic or Latino and Not Hispanic or Latino. There are five racial categories: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; and White.

1 Definitions for Ethnic and Racial Categories (OMB Directive 15)

The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. Reports of data on race and ethnicity will use these categories.

2 Ethnic Categories

Hispanic or Latino – A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

3 Racial Categories

American Indian or Alaska Native – A person having origins in any of the original peoples of North, Central or South America and who maintains tribal affiliation or community attachment.

Asian – A person having origins in any of the original peoples of the Far East, Southeast Asia or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam. (*Note*: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – A person having origins in any of the Black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander – A person having origins in any of the original peoples of Hawaii, Guam, Samoa or other Pacific Islands.

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

D *Updated Roles and Responsibilities for Implementing the Policy*

NIH staff provide educational opportunities for the extramural and intramural communities concerning this policy. In addition, staff are charged with monitoring the implementation of the policy during the development, review, award and conduct of research and manage the NIH research portfolio to comply with the policy. For specific guidance on the roles and reponsibilities of the PI, please refer to Appendix C: Amended NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.

The remaining sections of this workbook provide detailed information on the responsibilities of NIH program, review (including peer reviewers), grants management and contracts staff in implementing and ensuring compliance with the inclusion policy. Section 2 is devoted to implementation and procedures involving research grants, while Section 3 is devoted to implementation and procedures involving research contracts. Finally, Section 4 contains a list of resources available on the Internet regarding this policy. Although some of the following sections are directed to specific staff functional areas, it is important to remember that program, review, grants management and contracts each play a significant role and share in the responsibility for ensuring compliance. Understanding the role of your functional area and how it coordinates with others is encouraged.

Section 2

Research Grants:

How Does the Amended Policy Impact the Way NIH Does Business?

Research Grants: How Does the Amended Policy Impact the Way NIH Grantees Do Business?

I GRANT APPLICANTS PRE-SUBMISSION

A *Is It NIH-Defined Clinical Research?*

The Principal Investigator (PI), in discussions with program staff, should determine if the application involves clinical research, as defined by NIH policy (see section 1:II.A. in this document). The following discussion provides additional guidance in making this determination.

Additional Guidance

Research should be considered clinical research when the protocol involves either

1 Direct interaction between the investigator (or colleague) and living individuals or

2 Access to readily identifiable data that links directly to living individuals.

Readily identifiable data include any one of the following pieces of information: full name, address, birth date, social security number, financial account number, insurance policy number or unique coding that links directly to a living individual.

Some clinical research issues such as genetics, genetic testing and linkage to families are still evolving and present questions regarding the protection of human subjects that are the focus of ongoing scientific and ethical debate and discussion. Thus, this additional guidance on determining what is NIH clinical research may be updated in the future.

The examples can be used to further clarify when studies are or are not considered clinical research.

Examples of Patient-oriented Research

Case 1 PI proposes to collect specimens from living volunteers and conduct analyses on a cell protein process hypothesized as a potential mechanism of disease. Informed consent is obtained from the subjects, and data are stored with some readily identifiable information (i.e., data are easily linked back to the subject through subject's ID).

Is this clinical research? Yes – PI is interacting directly with subjects and is collecting and storing readily identifiable data.

Case 2 Similar to Case 1, PI proposes to collect specimens from living volunteers and conduct analyses on a cell protein process hypothesized as a potential mechanism of disease. Informed consent is obtained. However, the data are stored with no readily identifiable data (i.e., no subject ID, date or other information that can be linked directly to the individual).

Is this clinical research? Yes – PI is directly interacting with subjects. Although data are stored in an unlinked manner, the protocol involves direct contact with a live individual.

Case 3 PI proposes to obtain stem cells from a company on the NIH registry. The company does maintain records that link the cell lines to specific individuals (i.e., readily identifiable information). However, PI does not need access to the identifying information and the donor company is providing documentation that the identifying information will not be disclosed to PI.

Is this clinical research? No – PI has no interaction with a living person *and* has no access to readily identifiable information.

Case 4 PI proposes to obtain stem cells from a company listed on the NIH registry. The company does maintain records that link the cell lines to specific individuals (i.e., readily identifiable information). PI does not need access to the identifying information. However, PI has no documentation from the company that identifying information will not be disclosed.

Is this clinical research? Yes – PI has no interaction with a living person but does have access to readily identifiable information. PI would need to obtain a letter from the company assuring that the readily identifiable data will not be disclosed in order to consider this "not clinical research."

Case 5 PI proposes to obtain samples from a specimen bank. Because of the nature of the research question, readily identifiable information (e.g., birth date, home address) will be needed and will be obtained from the specimen bank. However, PI has no plans to make contact with a living donor.

Is this clinical research? Yes – Although PI is not directly interacting with individuals, PI has readily identifiable data.

Case 6 Similar to Case 5, PI proposes to obtain samples from a specimen bank, but the samples will all be from deceased individuals (e.g., brain bank). Readily identifiable information is available, and PI proposes to include this in the research.

Is this clinical research? No – PI has no interaction with a living individual. Access to readily identifiable data from deceased individuals is not considered clinical research.

Examples of Epidemiological, Behavioral, Health Services and Health Outcomes Research

Case 7 PI proposes to conduct secondary data analysis of epidemiological, behavioral or health services research. The initial data collection included readily identifiable information that is now part of the data set. However, PI has no plans for using the readily identifiable data or for re-contacting the subjects.

Is this clinical research? Yes – Although PI is not directly interacting with individuals, PI has access to readily identifiable data.

Case 8 PI proposes to conduct secondary data analysis of epidemiological, behavioral or health services data that are publicly available (e.g., census data) that have been stored without readily identifiable information in the data set. Also, PI will obtain documentation from the owner of the data set that no readily identifiable data will be disclosed to PI.

Is this clinical research? No – PI neither interacts with individuals nor has access to readily identifiable data.

Case 9 Similar to Case 8, PI proposes to conduct secondary data analysis of epidemiological, behavioral or health services data that have been stored without readily identifiable information in the data set. The owner of the data set, however, does have readily identifiable information on the subjects. PI has no documentation from the owner of the data set that the readily identifiable data will not be disclosed.

Is this clinical research? Yes – PI is not interacting with living individuals but could have access to readily identifiable data. Documentation would be needed from the owner of the data set stating that the readily identifiable information will not be disclosed in order to consider this "not clinical research."

What About the Human Subjects Exemptions?

It is important to remember that an exemption to human subjects protection indicates that the research is considered to present low risk of harm to the subjects. It does not mean that subjects are not human. Thus, it is possible that low-risk research, which is exempt from human subjects regulations, may still be considered clinical research.

Case 10 PI proposes research on normal educational practices and is not recording data in such a manner that identifies the human subjects (Human Subjects Exemption 1 & 2).

Is this clinical research? Yes – PI has direct interaction with living individuals.

Case 11 PI proposes research on existing data (biological and/or behavioral) that are publicly available and cannot be linked to the subjects (Human Subjects Exemption 4).

Is this clinical research? No – PI neither has contact with living individuals nor is working with readily identifiable data.

Case 12 PI proposes research to evaluate public benefits programs (Human Subjects Exemption 5).

Is this clinical research? Yes – PI is coming into direct contact with living individuals.

Case 13 PI proposes taste, food quality evaluations or consumer acceptance studies (Human Subjects Exemption 6).

Is this clinical research? Yes – PI is coming into direct contact with living individuals.

B *Guidance for Principal Investigators*

IF THE APPLICATION *INVOLVES CLINICAL RESEARCH,* PI SHOULD KNOW THAT:

a NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported clinical research.

b Inclusion must be addressed in developing the research design appropriate to the scientific objectives of the study.

c Inclusion is required unless:

1) Inclusion is inappropriate with respect to the health of the subjects;

2) Inclusion is inappropriate for the purpose of the study; or

3) Inclusion is inappropriate for some other reason, for which a compelling justification is made.

d Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources.

e Women of childbearing potential should *not* be excluded routinely from participation in clinical research.

f This policy applies to research subjects of all ages.

In the PHS 398 Instructions (5/01), the inclusion of women and minorities is now part of Section E: Human Subjects Research. PIs are instructed to include a section heading entitled "Inclusion of Women" and a separate section heading entitled "Inclusion of Minorities." No page limitation applies to this section, but PIs are encouraged to be succinct. These sections must provide information on the composition of the proposed study population in terms of sex/gender and racial/ethnic groups and provide a rationale for selection of such subjects in terms of the scientific objectives and proposed study design. The description should include (but is not limited to) information on the population characteristics of the disease or condition under study, national and local demography, knowledge of the racial/ethnic/cultural characteristics of the population, prior experience and collaborations in recruitment and retention of the populations and subpopulations to be studied, and the plans, arrangements and letters of commitment from relevant community groups and organizations for the planned study.

These sections *must* include the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design.
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group.
- The proposed dates of enrollment (beginning and end).
- A description of proposed outreach programs for recruiting women and minorities in clinical research as subjects.
- The proposed sample composition using the "5/01 Targeted/Planned Enrollment Format Page" and/or the "5/01 Enrollment Report Format Page."

If PI believes that the proposed research is *not clinical research yet does involve human subjects*, then PI should justify this position in the Human Subjects section of the application. There are no page limitations for this section; therefore PI may justify this position in as much detail as deemed appropriate.

C *Is It an NIH-Defined Phase III Clinical Trial?*

If the application contains an NIH-defined Phase III clinical trial (as defined in Section 2: I.A.1 above), then PI must address whether he/she expects to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

The research plan *must* include *one* of the following:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups (when prior studies strongly support these significant differences among subgroups).

or

- Plans to include and analyze sex/gender and/or racial/ethnic subgroups (when prior studies strongly support no significant differences in intervention effect between subgroups). (Representation of sex/gender and/or racial/ethnic groups as subject selection criterion is not required; however, inclusion and analyses are encouraged.)

or

- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups without requiring high statistical power for each subgroup (when the prior studies neither support nor rule out significant differences in intervention effect between subgroups.)

D *Implementing the New OMB Standards*

1 Impact on Data Collection

When an investigator is planning data collection items on ethnicity and race, categories identified in the definitions for "Ethnic and Racial Categories (OMB Directive 15)" should be used. (See item C.3 below).

Using self-report or self-identification to collect an individual's data on ethnicity and race, PI should use two separate questions with ethnicity information, followed by the option to select more than one racial designation. An example of this two-question format can be found in the PHS 398 Personal Data Form *(http://grants1.nih.gov/grants/funding/phs398/personal.pdf)*.

> **The 5/01 Targeted/Planned Enrollment Table Format Page**
> ***(http://grants1.nih.gov/grants/funding/phs398/enrollment.pdf)***
> **and 5/01 Inclusion Enrollment Report Table Format Page**
> ***(http://grants1.nih.gov/grants/funding/phs398/enrollment report.pdf)***
> **are *not* to be used for data collection from study participants.**

2 Impact on Reporting Data

When reporting these data in the aggregate, PI should report: (a) the number of respondents in each ethnic category; (b) the number of respondents who selected

only one category for each of the five racial categories; (c) the total number of respondents who selected multiple racial categories reported as the "number selecting more than one race"; and, (d) the number of respondents in each racial category who are Hispanic or Latino. PI may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as a comment section below the data table or as an attachment to the table. More detailed items should be designed in a way that they can be aggregated into the required categories for reporting purposes. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. Federal agencies will not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

3 The New Target and Enrollment Forms

PI should provide the following materials in the applications described in bold type.

a **New Applications (type 1), Competing Continuations (type 2), and Intramural Projects Submitting Applications Involving the Collection of New/Additional Data in Clinical Research:**

Investigators should provide plans for the total number of subjects proposed for the study, the distribution by ethnic/racial categories and sex/gender, and the study title. This information must be reported using the newly revised categories in OMB Directive 15 and according to the new format provided in the 5/01 Targeted/Planned Enrollment table. If there is more than one study, a separate table should be provided for each study. Any proposed racial/ethnic subpopulations should be listed below the table or as an attachment.

b **New Applications Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:**

For each study, investigators should provide plans for the total number of subjects proposed for the study and the distribution by ethnic/racial categories and sex/gender. Under these circumstances, PIs are not required to re-contact subjects solely to comply with the newly revised categories. If the existing data on ethnicity and race accurately correspond with the new categories in OMB Directive 15, PI can use the format in the 5/01 Targeted/Planned Enrollment table. However, if the existing data do not allow accurate correspondence with the new categories, then PI may report the information using the former categories and according to the format in the 4/98 version of the Inclusion Table
http://grants1.nih.gov/grants/funding/women_min/Inclusion Old_Form.pdf

II REVIEW CONSIDERATIONS

A *Applications That Fail to Address the Policy*

Prior to review, NIH staff should identify applications that fail to address the inclusion of women and minorities as subjects in clinical research. Failing to address the policy in an application may include either or both of the following:

- No description or section on the inclusion of women
- No description or section on the inclusion of minorities

The Scientific Review Administration (SRA) will contact the applicant and request that this information be provided prior to review. If applicants do not respond to this request for additional materials, the application may be deferred for review until the additional materials are provided.

B *Evaluation of Inclusion Description and Justifications for Clinical Research Grants*

During initial peer review, the Scientific Review Group (SRG) evaluates the proposed plan for the inclusion of women and minorities for appropriate representation or to evaluate the proposed justification when representation is limited or absent for each project involving human subjects in clinical research.

In evaluating inclusion plans, reviewers will provide a brief narrative to answer each of the following questions separately for women and minorities:

INCLUSION

- Does the applicant propose a plan for the inclusion of minorities and both sexes/genders for appropriate representation?
- How does the applicant address the inclusion of women and members of minority groups and their subpopulations in the development of a research design that is appropriate to the scientific objectives of the study?
- Does the research plan describe the composition of the proposed study population in terms of sex/gender and racial/ethic groups?
- Does the research plan provide a rationale for the selection and composition of subjects?

Exclusion

- Does the applicant propose justification when representation is limited or absent?
- Does the applicant propose exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects and/or with respect to the purpose of the research?

On the basis of the information provided in the application, reviewers evaluate the inclusion plans as "Absent," "Acceptable" or "Unacceptable."

SRAs should inform reviewers that when either the sex/gender inclusion plan and/or the minority inclusion plan are "Absent," reviewers should contact the SRA immediately. The SRA will determine if the application should be deferred for failing to address the inclusion policy.

1 Evaluating Sex/Gender Inclusion Plans

If the plans described in the inclusion of women section are judged "Unacceptable," then, the unacceptability must be reflected in the priority score assigned to the application. Criteria for unacceptable inclusion plans include:

- Representation that fails to conform to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research in relation to the scientific purpose of the study.
- The application provides insufficient information.
- The application does not adequately justify limited representation.

The sex/gender inclusion plan may be judged "Acceptable" based on one or more of the following:

- Both sexes/genders are included in the study in scientifically appropriate numbers.
- One sex/gender is excluded from the study because:
  - Inclusion of these individuals would be inappropriate with respect to their health;
  - The research question addressed is relevant to only one sex/gender;
  - Evidence from prior research strongly demonstrates no difference between sexes/genders; or
  - Sufficient data already exist with regard to the outcome of comparable studies in the excluded sex/gender and duplication is not needed in this study.

- One sex/gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by sex/gender (e.g., uniquely valuable stored specimens or existing datasets are single sex/gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
- Sex/gender representation of specimens or existing data sets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete sex/gender documentation are used), and this does not compromise the scientific objectives of the research.

2 Evaluating Minority Inclusion Plans

If the plans described in the inclusion of minorities section are judged "Unacceptable," the unacceptability must be reflected in the priority score assigned to the application. Criteria for unacceptable minority inclusion plans include:

- Representation that fails to conform to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research in relation to the scientific purpose of the study.
- The application provides insufficient information.
- The application does not adequately justify limited representation of minority groups or subgroups.
- The application does not realistically address recruitment/retention of minority groups or subgroups.

The minority inclusion plan may be judged "Acceptable" based on one or more of the following:

- Minority individuals are included in scientifically appropriate numbers.
- Some or all minority groups or subgroups are excluded from the study because:
  - Inclusion of these individuals would be inappropriate with respect to their health;
  - The research question addressed is relevant to only one racial or ethnic group;
  - Evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
  - A single minority group study is proposed to fill a research gap;
  - Significant data already exist with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

- Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
  - The size of study;
  - The relevant characteristics of the disease, disorder or condition;
  - The feasibility of making collaboration or consortium or other arrangements to include representation.
- Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
- Racial or ethnic origins of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

Note: Elements in evaluating minority inclusion are different from elements in the evaluation of sex/gender inclusion.

C *Evaluation of Inclusion Description and Justifications for NIH-Defined Phase III Clinical Trial Applications*

For NIH-defined Phase III clinical trials, the instructions to reviewers also include evaluation of the design and data analysis plans for examining intervention effects based on sex/gender and ethnicity/race differences.

1 The Sex/Gender Inclusion Plan May Be Judged "Acceptable" Based on One or More of the Following:

- Available evidence strongly indicates significant sex/gender differences of clinical or public health importance in intervention effect and the study design is appropriate to answer two separate primary questions – one for males and one for females – with adequate sample size for each sex/gender. *The research plan must include a description of plans to conduct analyses to detect significant differences in intervention effect*.

Remember: For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which depends upon the amount of information in the data set. With a very large amount of information, one could find a small but statistically significant difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential clinical importance that is not statistically significant.

- Available evidence strongly indicates there is no significant difference of clinical or public health importance between males and females in relation to the study variables. Representation of both sexes/genders is not required; however, inclusion of both sexes/genders is encouraged.

- There is no clear-cut scientific evidence to rule out significant differences of clinical or public health importance between males and females in relation to the study variables, and the study design includes sufficient and appropriate representation of both sexes/genders to permit valid analyses of differential intervention effect. *The research plan must include a description of plans to conduct the valid analysis of the intervention effect*.

  Remember: For the purpose of this policy, the term "valid analysis" 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 of the question of interest are:

  – Allocation of study participants of both sexes/genders (males and females) 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.

- One sex/gender is excluded from the study because:

  – Inclusion of these individuals would be inappropriate with respect to their health; or

– Inclusion of these individuals would be inappropriate with respect to the purposes of the research (e.g., the research question addressed is only relevant to one sex/gender).

2 The Minority Inclusion Plan May Be Judged "Acceptable" Based on One or More of the Following:

- Available evidence strongly indicates significant racial or ethnic differences of clinical or public health importance in intervention effect, and the study design is appropriate to answer separate primary questions for each of the relevant racial or ethnic subgroups, with adequate sample size for each. *The research plan must include a description of plans to conduct analyses to detect significant differences in intervention effect. (See definition of "significant differences" in Section 2: II.C.1.)*

- Available evidence strongly indicates there are no significant differences of clinical or public health importance among racial or ethnic groups or subgroups relation to the study variables. Minority representation is not required as a subject selection criterion; however, inclusion of minority group or subgroup members is encouraged.

- There is no clear-cut scientific evidence to rule out significant differences of clinical or public health importance among racial or ethnic groups or subgroups in relation to the effects of study variables, and the study design includes sufficient and appropriate representation of minority groups to permit valid analyses of differential intervention effect. *The research plan must include a description of plans to conduct the valid analysis of the intervention effect in subgroups. (See definition of "valid analyses" in Section 2: II.C.1.)*

- Some minority groups or subgroups are excluded from the study because:

  – Inclusion of these individuals would be inappropriate with respect to their health; or

  – Inclusion of these individuals would be inappropriate with respect to the purposes of the research (e.g., the research question addressed is not relevant to all subgroups).

D *Assignment of Sex/Gender and Minority Codes*

For single project applications, reviewers assign an overall code as described below. For multi-project applications, a code should be assigned to each individual project or subproject in an application containing multiple projects or involving distinct

populations or specimen collections. If only one project in a multi-project application involves clinical research, the codes assigned to that project will apply to the overall document; if there is more that one project covered by the policy, reviewers also assign an overall code to the entire application as follows:

1 Gender Codes

Format: Each code is a three-digit alphanumeric string:

- First character **G** (indicates sex/gender code)
- Second character **1, 2, 3,** or **4** (representation proposed in project – see below)
- Third character **A** or **U** (acceptable or unacceptable – see below)

Representation Proposed in Project (second character)

1 = both sexes/genders
2 = only women
3 = only men
4 = sex/gender unknown

Gender Codes (first character)

	Scientific Acceptability	
Gender Representation	***Acceptable***	***Unacceptable***
Both included	G1A	G1U
Women only	G2A	G2U
Men only	G3A	G3U
Unknown	G4A	G4U

Acceptability/Unacceptability of Representation of Women (third character)

A = Representation is scientifically acceptable and recruitment/retention has been realistically addressed, or an acceptable justification for exclusion has been provided.

U = Representation is unacceptable. Application fails to conform to NIH policy guidelines in relation to the scientific purpose of the study, fails to provide sufficient information, does not adequately justify exclusion of women subjects, or does not realistically address recruitment/retention.

2 Minority Codes

The inclusion of racial/ethnic groups should be determined by the scientific questions under examination and their relevance to racial and ethnic groups. Applications should describe the subgroups that will be included in the research. It is not anticipated that every study will include all minority groups and subgroups.

In foreign research projects involving clinical research, the definition of minority groups may be different than in the United States; if there are scientific reasons for examining minority group or subgroup differences in such settings, studies should be designed to accommodate such differences.

Format: Each code is a three-digit alphanumeric string:

- First character **M** (indicated minority code)
- Second character **1, 2, 3, 4,** or **5** (representation proposed in project – see below)
- Third character **A** or **U** (scientifically acceptable or unacceptable – see below)

Representation Proposed in Project (second character)

1 = minority and non-minority
2 = only minority
3 = only non-minority
4 = minority representation unknown
5 = only foreign subjects in study population (no U.S. subjects). If the study population includes both foreign and U.S. study subjects then use codes 1 thru 4 to describe the U.S. component (do not use code 5).

Acceptability/Unacceptability of Representation of Minorities (third character)

A = Representation is scientifically acceptable and recruitment/retention has been realistically addressed, or an acceptable justification for exclusion has been provided.

U = Representation is unacceptable. Application fails to conform to NIH policy guidelines in relation to the scientific purpose of the study, fails to provide sufficient information, does not adequately justify exclusion of minority consideration in subjects, or does not realistically address recruitment/retention.

Minority Codes

Minority Representation	Scientific Acceptability	
	Acceptable	*Unacceptable*
Minorities and Non-minorities included	M1A	M1U
Minorities only	M2A	M2U
Non-minorities	M3A	M3U
Unknown	M4A	M4U
Foreign	M5A	M5U

E *Human Subjects Codes vs. Sex/Gender and Minority Codes*

PIs should remember that the comments and coding in reference to human subjects protections are separate from the comments and coding in reference to the inclusion of women and minorities in clinical research.

1 Human Subjects Research Codes

In the human subjects research section of the PHS 398, applicants must address the involvement of human subjects and protections from research risk relating to their participation in the proposed research plan. Exemption codes are used to claim an exemption from the human subjects regulations. Also, reviewers indicate whether the proposed research raises human subjects concerns (coded as a 44 by the SRA) or if no concerns were raised by the reviewers.

The exemption code and human subjects concern code are indicated on the summary statement. The coding information is entered into IMPAC II by review staff.

2 Sex/Gender and Minority Representation Codes

Also in the human subjects research section, if the research is clinical research, applicants must address the representation and involvement of women and minorities in the research. Reviewers evaluate the scientific acceptability of the inclusion plans and use the gender and minority codes in this evaluation.

Sex/Gender codes and minority codes are separate from human subject concerns and exemptions.

Sex/Gender and minority codes are indicated on the summary statement. The coding information is entered into IMPAC II by review staff.

F *NIH-Defined Phase III Clinical Trials Coding*

Review also serves a vital role in determining whether the proposed research is:

- **Yes** – an NIH-defined Phase III clinical trial;
- **No** – not a Phase III trial, but is clinical research;
- **X** – not clinical research or is unscored and does not require sex/gender and/or minority codes.

Determination of this code is the responsibility of the review staff, based on information in the application, discussions at the review meeting, and their knowledge of the field. The Phase III clinical trial code is indicated on the summary statement. The coding information is entered into IMPAC II by review staff.

III PROGRESS REPORTS

A *Policy Statement*

Research awards covered by this policy require an annual progress report on enrollment of women and men, and on the race and ethnicity of research participants so that accrual can be monitored. Progress reports must contain information on research progress, which includes research participant enrollment and retention. Progress and/or final analyses based on sex/gender, race/ethnicity and relevant subpopulation differences are encouraged for all clinical research awards and are required for NIH-defined Phase III clinical trials. NIH has the authority to delay, withhold, remove expanded authorities or terminate an award that does not comply with the inclusion policy.

B *Final Progress Report*

A final progress report is required within 90 days of the end of grant support unless an extension is issued by the grants management staff. The final progress report for clinical research studies is required to include a summary of the final cumulative enrollment of subjects by sex/gender and race/ethnicity.

Failure to provide accurate and timely final reports may affect the future funding to your organization or awards with the same investigators. NIH has the authority to delay funding of subsequent awards to the organization or investigator until satisfactory information is received.

For *NIH-defined Phase III clinical trials*, the final progress report also must include final analyses of intervention effect by sex/gender and race/ethnicity or provide a justification and plan for ensuring completion of these analyses and reporting to NIH. Failure to provide these analyses may affect the future funding to the organization or awards to the PI. NIH has the authority to delay funding of subsequent awards to the organization or investigator until satisfactory information is received.

Section 3

Research Contracts:

How Does the Amended Policy Impact

the Way NIH Does Business?

Research Contracts: How Does the Amended Policy Impact the Way NIH Does Business?

I ACQUISITION PLANNING AND PROPOSAL SUBMISSION

Program Staff/Project Officers, Contracting Officers and Offerors

A *Is the Contract for Clinical Research?*

The contract specialist and the program staff/project officer will discuss the requirement during the acquisition planning phase to determine whether the acquisition is for NIH-defined clinical research. The following provides additional guidance in making this determination.

Additional Guidance

Research will be considered "clinical research" when the protocol/acquisition involves *either* direct interaction between the investigator (or colleague) and living individuals *or* access to readily identifiable data that links directly to living individuals.

"Readily identifiable data" includes any one of the following pieces of information: full name, address, birth date, social security number, financial account number, insurance policy number or unique coding that links directly to a living individual.

Note: Some clinical research issues such as genetics, genetic testing and linkage to families are evolving and present questions regarding the protection of human subjects that are the focus of scientific debate and discussion. Thus, this additional guidance on determining what is NIH clinical research may be updated in the future.

The following examples further clarify when studies are or are not considered clinical research.

Examples of Patient-Oriented Research

Case 1 The principal investigator (PI) will collect specimens from living volunteers and conduct analyses on a cell protein process hypothesized as a potential mechanism of disease. Informed consent is obtained from the subjects, and data are stored with some readily identifiable information (i.e., data are easily linked back to the subject through subject's ID).

Is this clinical research? Yes – PI is interacting directly with subjects and is collecting and storing readily identifiable data.

Case 2 Similar to Case 1, PI will collect specimens from living volunteers and conduct analyses on a cell protein process hypothesized as a potential mechanism of disease. Informed consent is obtained. However, the data are stored with no readily identifiable data (i.e., no subject ID, date or other information that can be linked directly to the individual).

Is this clinical research? Yes – PI is directly interacting with subjects. Although data are stored in an unlinked manner, the protocol involves direct contact with a live individual.

Case 3 PI will obtain stem cells from a company on the NIH registry. The company does maintain records that link the cell lines to specific individuals (i.e., readily identifiable information). However, PI does not need access to the identifying information *and* the donor company is providing documentation that the identifying information will not be disclosed to PI.

Is this clinical research? No – PI has neither interaction with a living person nor access to readily identifiable information.

Case 4 PI will obtain stem cells from a company listed on the NIH registry. The company does maintain records that link the cell lines to specific individuals (i.e., readily identifiable information). PI does not need access to the identifying information. However, PI has no documentation from the company that identifying information will not be disclosed.

Is this clinical research? Yes – PI has no interaction with a living person but does have access to readily identifiable information. PI would need to obtain a letter from the company assuring that the readily identifiable data will not be disclosed in order to consider this "not clinical research."

Case 5 PI will obtain samples from a specimen bank. Because of the nature of the research, readily identifiable information (e.g., birth date, home address) will be needed and will be obtained from the specimen bank. However, PI has no plans to make contact with a living donor.

Is this clinical research? Yes – Although PI is not directly interacting with individuals, PI has readily identifiable data.

Case 6 Similar to Case 5, PI will obtain samples from a specimen bank, but the samples will all be from deceased individuals (e.g., brain bank). Readily identifiable information is available, and PI proposes to include this in the research.

Is this clinical research? No – PI has no interaction with a living individual. Access to readily identifiable data from deceased individuals is not considered clinical research.

Examples of the Epidemiological, Behavioral, Health Services and Health Outcomes Research

Case 7 PI will conduct secondary data analysis of epidemiological, behavioral or health services research. The initial data collection included readily identifiable information that is now part of the data set. However, PI has no plans for using the readily identifiable data or for re-contacting the subjects.

Is this clinical research? Yes – PI is not directly interacting with individuals, but does have access to readily identifiable data.

Case 8 PI will conduct secondary data analysis of epidemiological, behavioral or health services data that are publicly available (e.g., census data) that have been stored without readily identifiable information in the data set. Also, PI will obtain documentation from the owner of the data set that no readily identifiable data will be disclosed to PI.

Is this clinical research? No – PI neither interacts with individuals nor has access to readily identifiable data.

Case 9 Similar to Case 9, PI will conduct secondary data analysis of epidemiological, behavioral or health services data that have been stored without readily identifiable information in the data set. The owner of the data set, however, does have readily identifiable information on the subjects. PI has no documentation from the owner of the data set that the readily identifiable data will not be disclosed.

Is this clinical research? Yes – PI is not interacting with living individuals but could have access to readily identifiable data. Documentation would be needed from the owner of the data set stating that the readily identifiable information will not be disclosed in order to consider this "not clinical research."

What About the Human Subjects Exemptions?

It is important to remember that an exemption to human subjects research designates that the research is considered to pose a low risk of harm to the subjects. *It does not mean that subjects are not human*. Thus, it is possible that low-risk research, which is exempt from human subjects regulations, may still be considered clinical research.

Case 10 PI will conduct research on normal educational practices and is not recording data in such a manner that identifies the human subjects (Human Subjects Exemption 1 & 2).

Is this clinical research? Yes – PI has direct interaction with living individuals.

Case 11 PI will conduct research on existing data (biological and/or behavioral) that are publicly available and cannot be linked to the subjects (Human Subjects Exemption 4).

Is this clinical research? No – PI neither has contact with living individuals nor is working with readily identifiable data.

Case 12 PI will conduct Departmental research to evaluate public benefits programs (Human Subjects Exemption 5).

Is this clinical research? Yes – PI has direct contact with living individuals.

Case 13 PI will perform taste, food quality evaluations or consumer acceptance studies (Human Subjects Exemption 6).

Is this Clinical Research? Yes – PI has direct contact with living individuals.

1 If the Acquisition Is for Clinical Research

If it is determined that the acquisition is for clinical research, then the resultant acquisition plan/request for contract will so state and the resultant solicitation/ request for proposals will inform prospective offerors of the following requirements:

a NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported clinical research.

b Inclusion must be addressed in developing the technical proposal appropriate to the scientific objectives of the study.

c Inclusion is required unless:

1) Inclusion is inappropriate with respect to the health of the subjects;

2) Inclusion is inappropriate for the purpose of the study; and/or

3) Inclusion is inappropriate for some other reason, for which a justification is made.

d Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources.

e Women of childbearing potential should not be excluded routinely from participation in clinical research.

f This policy applies to research subjects of all ages.

In a separate section of the technical proposal (entitled "Human Subjects," and which should encompass all human subjects issues) the offeror must provide information on the composition of the proposed study population in terms of sex/gender and racial/ethnic groups and provide a rationale for selection of such subjects in

terms of the scientific objectives of the acquisition. The description should include (but is not limited to) information on the population characteristics of the disease or condition under study, national and local demography, knowledge of the racial/ethnic/cultural characteristics of the population, prior experience in recruitment and retention of the populations and subpopulations to be studied, and the plans, arrangements and letters of commitment from relevant community groups and organizations.

This section of the technical proposal must include the following information:

- A description of the subject selection criteria and rationale for selection in response to the statement of work in the request for proposals, or in terms of the scientific objectives and proposed study design.
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group.
- The proposed dates of enrollment (beginning and end).
- A description of proposed outreach programs for recruiting women and minorities in clinical research as subjects.
- The proposed sample composition using the 5/01 "Targeted/Planned Enrollment Table" (modified in the NCI Workform 10/01) and/or the 5/01 "Inclusion Enrollment Report " (modified in the NCI Workform 10/01). (See NCI RFP workform – section J, attachments at *http://rcb.cancer.gov/rcb-internet/forms/forms.htm.*)

2 If the Acquisition Is Not Clinical Research Yet Involves Human Subjects

If the offeror believes that the proposed research is not clinical research yet does involve human subjects, the offeror must justify this position in the section on human subjects in the technical proposal. The offeror must explain its rationale in as much detail as deemed appropriate.

B *Is the Contract for an NIH-Defined Phase III Clinical Trial?*

If the acquisition is for an NIH-defined Phase III clinical trial (see section 1: II.B. in this document), the solicitation will inform prospective offerors that the separate section of the technical proposal must contain the elements stated in section 3: I.A.1 above *and* address whether the offeror expects to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The proposal may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

The proposal *must* include *one* of the following elements:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups *when prior studies strongly support these significant differences among subgroups*.

or

- Plans to include and analyze sex/gender and /or racial/ethnic subgroups *when prior studies strongly support no significant differences in intervention effect between subgroups*. (Representation of sex/gender and/or racial/ethnic groups as subject selection criterion is not required; however, inclusion and analyses are encouraged.)

or

- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) *when the prior studies neither support nor negate significant differences in intervention effect between subgroups*.

C *Implementing the New OMB Standards*

1 Impact on Data Collection

When an investigator is planning data collection items on ethnicity and race, categories identified in the definitions for ethnic and racial categories (OMB Directive 15) should be used. (See item C.3 below.)

Using self-report or self-identification to collect an individual's data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation. An example of this two-question format can be found in the PHS 398 Personal Data Form (http://grants.nih.gov/grants/funding/phs398/personal.pdf).

> **The 5/01 Targeted/Planned Enrollment Table (modified in the NCI Workform 10/01) and 5/01 Inclusion Enrollment Report (modified in the NCI Workform 10/01, Attachment J – *http://rcb.cancer.gov/rcb-internet/forms/forms.htm*) are *not* to be used by the principal investigator for data collection from study participants.**

2 Impact on Reporting Data

When reporting these data in the aggregate, investigators should report (a) the number of respondents in each ethnic category; (b) the number of respondents who selected only one category for each of the five racial categories; (c) the total number of respondents who selected multiple racial categories reported as the "number selecting more than one race"; and (d) the number of respondents in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. More detailed items should be designed in a way that they can be aggregated into the required categories for reporting purposes. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. Federal agencies will not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

3 The New Target and Enrollment Forms

Offerors should provide the following materials in the proposals described in bold type.

a **Proposals Involving the Collection of New/Additional Data in Clinical Research**

For each study, offerors should provide plans for the total number of subjects proposed, the distribution by ethnic/racial categories and sex/gender, and the study title. For each study, a separate table should be provided. This information must be reported using the newly revised categories required by OMB Directive 15 and according to the new format provided in the 5/01 Targeted/Planned Enrollment Table (modified in the NCI Workform 10/01) (See NCI RFP Workform at *http://rcb.cancer.gov/rcb-internet/forms/forms.htm*). Any proposed racial/ethnic subpopulations should be listed below the Targeted/Planned Enrollment Table.

b **Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data**

For each study, offerors should provide plans for the total number of subjects proposed and the distribution by ethnic/racial categories and sex/gender. Contracting officers or their designees should advise offerors that under these circumstances, they are not required to re-contact subjects solely to comply with the newly revised categories. If the existing data on ethnicity and race accurately corresponds with the new categories in OMB Directive 15, the offeror can use the format in the 5/01 Targeted/Planned Enrollment Table (modified in the NCI Workform 10/01). However, if the existing data do not allow accurate correspondence with the new categories, the offeror may report the information

using the former categories and according to the format in section J of the NCI Workform at *http://rcb.cancer.gov/rcb-internet/forms/forms.htm* in the form entitled "Annual Technical Progress Report Format for Each Study."

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html – NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research.

II TECHNICAL REVIEW/EVALUATION CONSIDERATION

SRA, Technical Reviewers and Program Staff/Project Officers

A *Evaluation of Inclusion Description and Justifications for Clinical Research Contract Proposals*

Proposals will be evaluated in accordance with the technical evaluation criteria set forth in the solicitation. During initial peer review, the Scientific Review Group (SRG) evaluates the proposed women and minorities inclusion plan for appropriate representation or the proposed justification for limiting or excluding representation.* In evaluating inclusion plans, reviewers will provide a brief narrative as applicable to answer each of the following questions separately for women and minorities:

1 Inclusion

- Does the offeror propose a plan for the inclusion of minorities and both sexes/genders for appropriate representation?
- How does the offeror address the inclusion of women and members of minority groups and their subpopulations in the development of a proposal that addresses the requirements of the statement of work, or is appropriate to the scientific objectives of the research?
- Does the proposal describe the composition of the proposed study population in terms of sex/gender and racial/ethic group?
- Does the proposal provide a rationale for the selection and composition of subjects?

2 Exclusion

- Does the offeror propose justification when representation is limited or absent?
- Does the offeror propose exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects and/or with respect to the purpose of the research?

** The Scientific Review Group is also known as the Technical Evaluation Group (TEG).*

On the basis of the information provided in the proposal, reviewers rate the inclusion plans as "Acceptable" or "Unacceptable."

Evaluating Sex/Gender Inclusion Plans

If the sex/gender inclusion plan is judged "Unacceptable", then the narrative must explain the rationale. Criteria for unacceptable inclusion plans include:

- Representation that fails to conform to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research in relation to the scientific purpose of the study.
- The proposal provides insufficient information, or discussion regarding inclusion of women is absent.
- The proposal does not adequately justify limited representation.

The sex/gender inclusion plan may be judged "Acceptable" based on one or more of the following:

- Both sexes/genders are included in the study in scientifically appropriate numbers.
- One sex/gender is excluded from the study because:
  - Inclusion of these individuals would be inappropriate with respect to their health;
  - The statement of work and/or the proposal in response to the solicitation is relevant to only one sex/gender;
  - Evidence from prior research strongly demonstrates no difference between sexes/genders;
  - Sufficient data already exist with regard to the outcome of comparable studies in the excluded sex/gender and duplication is not needed in this study.
- One sex/gender is excluded or severely limited because the objective of the solicitation constrains the offeror's selection of study subjects by sex/gender (e.g., uniquely valuable stored specimens or existing datasets are single sex/gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
- Sex/gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or datasets with incomplete sex/gender documentation are used), *and* this does not compromise the scientific objectives of the research.

Evaluating Minority Inclusion Plans

If the minority inclusion plan is judged "Unacceptable", then the narrative must explain the rationale. Criteria for unacceptable minority inclusion plans include:

- Representation that fails to conform to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research in relation to the scientific purpose of the acquisition.
- The proposal provides insufficient information, or discussion regarding the minority inclusion plan is absent.
- The proposal does not adequately justify limited representation of minority groups or subgroups.
- The proposal does not realistically address recruitment/retention of minority groups or subgroups.

The minority inclusion plan may be judged "Acceptable" based on one or more of the following:

- Minority individuals are included in scientifically appropriate numbers.
- Some or all minority groups or subgroups are excluded from the study because:
  - Inclusion of these individuals would be inappropriate with respect to their health;
  - The research required by the statement of work is relevant to only one racial or ethnic group; and/or
  - Evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables.
- A single minority group study is proposed to fill a research gap.
- Significant data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.
- Some minority groups or subgroups are excluded or poorly represented because the geographical location where the work is to be performed has only limited numbers

of these minority groups who would be eligible for the study, *and* the offeror has satisfactorily addressed this issue in terms of:

  – The size of study;

  – The relevant characteristics of the disease, disorder or condition; and/or

  – The feasibility of making a collaboration or consortium or other arrangements to include representation.

- Some minority groups or subgroups are excluded or poorly represented because the purpose of the acquisition constrains the offeror's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).

- Racial or ethnic origins of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) *and* this does not compromise the scientific objectives of the acquisition.

Note: Elements in evaluating minority inclusion are different from elements in the evaluation of sex/gender inclusion.

B ***Evaluation of Inclusion Descriptions and Justifications for NIH-Defined Phase III Clinical Trial Proposals***

For NIH-defined Phase III clinical trials, the reviewers must also evaluate the design and data analysis plans for examining intervention effects based on sex/gender and ethnicity/race differences.

The sex/gender inclusion plan may be judged "Acceptable" based on one or more of the following criteria:

- Available evidence strongly indicates significant sex/gender differences of clinical or public health importance in intervention effect and the study design is appropriate to answer two separate primary questions – one for males and one for females – with adequate sample size for each sex/gender. *The proposal must include a description of plans to conduct analyses to detect significant differences in intervention effect.* (See definition of "significant differences" in Section 2:II.C.1.)

- Available evidence strongly indicates there is no significant difference of clinical or public health importance between males and females in relation to the study variables. Representation of both sexes/genders is not required: however, inclusion of both sexes/genders is encouraged. *Note*: The inclusion of both sexes/genders may be required by the statement of work; in this case, the proposal must address such inclusion.

- There is no clear-cut scientific evidence to rule out significant differences of clinical or public health importance between males and females in relation to the study variables, and the study design includes sufficient and appropriate representation of both sexes/genders to permit valid analyses of differential intervention effect. *The proposal must include a description of plans to conduct the valid analysis of the intervention effect.* (See definition of "valid analysis" in section 2:II.C.1.)

- One sex/gender is excluded from the study because:

  – Inclusion of these individuals would be inappropriate with respect to their health, or

  – Inclusion of these individuals would be inappropriate with respect to the purposes of the research (e.g., the research question addressed is only relevant to one sex/gender).

The minority inclusion plan may be judged "Acceptable" based on one or more of the following:

- Available evidence strongly indicates significant racial or ethnic differences of clinical or public health importance in intervention effect and the proposal is appropriate to answer separate primary questions for each of the relevant racial or ethnic subgroups, with adequate sample size for each. *Note*: This only applies if the sample size is not dictated by the statement of work. *The proposal must include a description of plans to conduct analyses to detect significant differences in intervention effect.* (See definition of "significant differences" in section 2:II.B.1.)

- Available evidence strongly indicates there are no significant differences of clinical or public health importance among racial or ethnic groups or subgroups in relation to the study variables. Minority representation is not required as a subject selection criterion unless required by the statement of work; however, inclusion of minority group or subgroup members is encouraged.

- There is no clear-cut scientific evidence to rule out significant differences of clinical or public health importance among racial or ethnic groups or subgroups in relation to the effects of study variables and the proposal includes sufficient and appropriate representation of minority groups to permit valid analyses of differential intervention effect. *The proposal must include a description of plans to conduct the valid analysis of the intervention effect in subgroups.* (See definition of "valid analyses" in section 2:II.B.2)

- Some minority groups or subgroups are excluded from the study because:

  – Inclusion of these individuals would be inappropriate with respect to their health; or

  – Inclusion of these individuals would be inappropriate with respect to the purposes of the research (e.g., the statement of work in the solicitation is not relevant to all subgroups).

C *Program/Project Officer Review of the Appropriateness of the Target Data*

After the SRG/TEG review and comments, it is the responsibility of program/project officer staff, in conjunction with the contracting officer, to evaluate the appropriateness of the proposed targeted/planned enrollment data based on their knowledge of the field. When reviewing the appropriateness of the proposed target data, NIH program/project officer staff may consider and provide a narrative discussion on one or more of the following points:

- Does the proposed number/proportions of women/men and different racial groups correspond to the population characteristics of the disease and/or is the proposed number/proportions in compliance with the requirements of the statement of work?

- Is there a compelling rationale for proposed exclusion of any sex/gender or ethnic/racial group?

- Is this a follow-up of a pre-existing cohort that provides unique information/ opportunity about the focus of study?

See Section 3: III.A.1 regarding discussions with offerors to resolve any issues raised by either the SRG/TEG or the program staff/project officer during review of proposed target/planned enrollment data.

D *Confirming the Analysis Plans for NIH-Defined Phase III Clinical Trials*

NIH-defined Phase III clinical trials must include plans for valid analysis of sex/gender and ethnicity/race differences. It is the responsibility of program/project officer staff, based on the comments from the SRG/TEG and their knowledge of the field, to confirm the appropriateness of the proposed plans for conducting sex/gender and/or racial/ethnic analysis plans for NIH-defined Phase III clinical trials, in conjunction with the proposed distribution of sex/gender and race/ethnicity in the target data.

See Section 3, C.1.a regarding discussions with offerors to resolve any issues raised by either the SRG/TEG or the program staff/project officer during review of analysis plan.

E *Human Subjects Comments/Evaluations vs. Sex/Gender and Minority Comments/Evaluations*

It is important for reviewers, SRAs, and program/project officers to remember that the comments/evaluations in reference to human subjects protections are separate from the comments/evaluations in reference to the inclusion of women and minorities in clinical research.

III GENDER/MINORITY ISSUES

Process of Review and Resolution Is Needed Prior to Award

A *Award Decisions – Contracting Officers*

1 Negotiation and Revision

Proposals with unacceptable inclusion plans receive an "Unacceptable" sex/gender or minority rating. These proposals may not be funded until NIH is assured of acceptability/appropriateness of these plans from the offerors.

Typically, if the proposal is otherwise acceptable, the issues raised by the SRG/TEG and program/project officers will be brought to the attention of the offeror during discussions and the offeror will be afforded an opportunity to discuss, clarify or modify the plan during the discussions and in its final proposal revision. If the discussion results in any changes to the plan or the data in the Targeted/Planned Enrollment Table, and, for NIH-defined Phase III clinical trials, to the plans for valid analysis of sex/gender and ethnicity/race differences, the offeror should submit a revised table/plan and any supporting documentation. The revised table/plan should be included as part of the contract file.

If the plan is still considered "Unacceptable" by the Government after discussions, the offeror may not be considered further for award.

Note: NIH-defined Phase III clinical trials must include plans for valid analysis of sex/gender and ethnicity/race differences. It is important for program staff and project officers to review and evaluate the adequacy of these plans, in conjunction with the proposed distribution of sex/gender and race/ethnicity in the target data, and for the contracting officer to discuss/resolve any issues with the offeror prior to award. Any substantive changes that result from these discussions should be documented in the contract file.

2 Contract Award Language

At the time of award, the contract shall include the following language:

"Annual Technical Progress Report for Clinical Research Study Populations

The Contractor shall submit information about the inclusion of women and members of minority groups and their subpopulations for each study being performed under this contract. This information shall be submitted in the format indicated in the attachment entitled, "Inclusion Enrollment Report," which is set forth in Section J of this contract. This format, modified to indicate that it is a final report, shall also be used for reporting purposes in the final report. The report shall be submitted in accordance with ARTICLE F.1. DELIVERIES of this contract. In addition, the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended, October, 2001 applies. If this contract is for Phase III clinical trials, see II.B of these guidelines. The Guidelines may be found at the following website:*

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

A description of the plans to conduct analyses, as appropriate, by sex/gender and/or racial/ethnic groups shall be included in the clinical trial protocol as approved by the IRB, and a description of the progress in the conduct of these analyses, as appropriate, must be reported in the annual progress report and the final report. If the analysis reveals no subset differences, a brief statement to that effect, indicating the subsets analyzed, will suffice. Inclusion of the results of subset analysis is strongly encouraged in all publication submissions. The final report must include all final analyses of the data on sex/gender and race/ethnicity."

Note: *For Level of Effort Contracts, replace this sentence with the following. *"[The first report shall be due__. Thereafter, the report shall be due on or before the (Working/Calendar) day following each reporting period. The final report shall be due on__.]"*

B *Monitoring of Information in Progress Report*

1 Policy Statement

Contracts covered by this policy require the contractor to report annually on enrollment of women and men and on the race and ethnicity of research participants so that accrual can be monitored. Annual progress reports submitted by the principal investigator must contain information on research progress, including research participant enrollment and retention. Progress and/or final analyses based on sex/gender and race/ethnicity differences are encouraged for all clinical research contracts and are required for all NIH-defined Phase III clinical trials. NIH has the authority to terminate a contract that does not comply with the inclusion policy in terms of providing the required reports and/or in meeting its planned enrollment goals.

2 Annual Inclusion Enrollment Report

Contractors must include yearly inclusion enrollment reports that describe the actual cumulative accrual of study populations and the sex/gender and ethnicity/race distributions.

For most contracts awarded in FY 02, investigators will be completing the *5/01 Inclusion Enrollment Report* that reflects the new OMB standards for reporting data on race and ethnicity. The table on the 5/01 Inclusion Enrollment Report contains two parts; part A is for all subjects and part B is for Hispanics or Latinos. The investigator should provide contract title, total enrollment (from target), protocol number (if available), and contract number. For Part A the investigator should provide the distribution of subjects by ethnic and racial categories and by sex/gender according to the format in the 5/01 Inclusion Enrollment Report. Part B should include information on the race of all Hispanics (or Latinos) enrolled in Part A. If there is more than one study, the investigator should provide a separate table for each study. Also, if a study involves both domestic and foreign populations, separate tables should be provided – one for domestic and one for foreign. Any table including information on foreign populations should be asterisked and footnoted, indicating the involvement of foreign participants. For tables containing either domestic or foreign data, any proposed racial/ethnic subpopulations should be listed below the table.

For progress reports for contracts that began data collection prior to FY02, investigators may report ethnicity/race and sex/gender sample composition using either the format in the former "Annual Technical Progress Report Format for Each Study" found in section J of the NCI Workform at *http://rcb.cancer.gov/rcb-internet/forms/forms.htm*, *or* the new 5/01 Inclusion Enrollment Report (modified in the NCI Workform 10/01). Deciding which format is acceptable depends on the following:

- The 5/01 Inclusion Enrollment Report (modified in the NCI Workform 10/01) should be used if the investigator is collecting data from subjects that comply with the new OMB Directive 15 standards, i.e., is using, at a minimum, a two-question format (with one question asking about ethnicity and the other asking about race) *and* allowing the participant to indicate more than one race.

- The former "Annual Technical Progress Report Format for Each Study" should be used if the investigator is still collecting data using the former standards, i.e., using a one-question format to ask about ethnicity and race, and *not* allowing participants to select more than one race.

  Note: Trying to "fit" data collected using the former standards into the new format is not recommended. The investigator will not have the race information for the Hispanic/Latino section of the table *and* will not have data that corresponds to the new racial categories. If program staff suspect this may have occurred, they should contact the investigator, clarify the appropriate format for the data, and, if necessary, receive a revised enrollment table from the investigator.

- Once an investigator begins use the new inclusion enrollment report, they must continue using this format for the remaining years of the contract.

In filling out the Inclusion Enrollment report, the investigator should not assume or guess a subject's racial or ethnic affiliation. The investigator should collect the data using instruments that allow respondents to select their racial or ethnic affiliation separately.

3 Project Officer Review of Annual Enrollment Data

The project officer will evaluate annual progress reports to determine if sex/gender and/or minority information has been provided and if recruitment/retention is appropriate in accordance with the terms of the contract and is on schedule. The progress report will be evaluated for the description of subject recruitment/retention and study composition. The Inclusion Enrollment report will be evaluated for the numerical distribution of subjects by sex/gender and ethnicity/race.

4 Missing, Inappropriate or Inconsistent Information

If the project officer notes missing information or considers the information in either the progress report text, inclusion enrollment report or both to be inappropriate or inconsistent with the proposed target data and/or stage of data collection, he/she should contact the contracting officer, who will discuss and resolve the issues with the contractor. A summary of the discussion and resolution should be included in the contract file.

For NIH-defined Phase III clinical trials, the information in the progress report should also indicate if any data analysis has begun for the trial and, if so, what progress has been made in conducting valid analyses for sex/gender and race/ethnicity differences. If this information is missing or considered inconsistent with the proposed data analysis plan and/or stage of data collection, the project officer should contact the contracting officer who will discuss and resolve the issues with the contractor. Also, a summary of the discussion and resolution should be included in the contract file.

5 Review of the Final Progress Report

Contractors are required to submit a final progress report no later than the expiration date of the contract. (*Note*: The contract may require a draft report at an earlier date). The final progress report for contracts for clinical research is required to include a summary of the final cumulative enrollment of subjects by sex/gender and race/ethnicity.

The project officer should review the final progress report and determine if the final cumulative enrollment data is appropriate. If the project officer has any questions about these data, he/she should notify the contracting officer to contact the Principal Investigator to provide any changes. Any changes recorded in the final progress report. All final accrual of subjects must be entered into the population tracking system and designated as "final" data.

Failure to provide accurate and timely final reports may affect the contractor's past performance rating as well as any future funding of contract awards. If the project officer identifies such problems with the final report, these problems and potential corrective actions should be discussed with the contracting officer, and the project officer may also provide information on such problems in the contractor's past performance evaluation.

For NIH-defined Phase III clinical trials, the final progress report also must include final analyses of intervention effect by sex/gender and race/ethnicity. Failure to provide these analyses may affect the contractor's past performance rating as well as any future fund of contract awards. If the project officer identifies such problems with the final report, the problems and potential corrective actions should be discussed with the contracting officer and the project officer may also provide information regarding such problems in the contractor's past performance evaluation.

Section 4

Recruitment and Retention of Women and Minorities in Clinical Research: Elements of Outreach

Recruitment and Retention of Women and Minorities in Clinical Research: Elements of Outreach

I INTRODUCTION

For many clinical investigators, the pathway from conceptualization through study completion is fraught with delirious highs and dreadful lows. The first challenge, getting a study funded, is followed quickly by the challenge of recruiting and retaining appropriate sex/gender representation, as well as research participants from diverse population groups. This section focuses on the successful recruitment, inclusion, and retention of women and minority subjects in clinical research. It highlights barriers to participation in clinical research and provides information on five elements of recruitment and retention that may assist investigators to best accrue recruitment and retention of women and minorities. It also provides a table of selected recruitment and retention strategies and tips. The section closes with findings pertaining to successful cases of recruitment and retention of women and minorities in clinical research. Successful recruitment of diverse population groups often begins with culturally and racially sensitive outreach into the communities in which individuals reside. Ideally, community outreach for research purposes should be part of the overall goal of the research institution and not solely the province of individual investigators.

II BACKGROUND

Historically, the typical and usual research participant was a white male. This legacy exists for many and varied reasons. History, education, culture, language, income and wealth, geography, racial identity, prejudice, paternalism and other social deterrents are implicated in the underrepresentation of women and minorities in clinical research (Millon Underwood, 2000; Giuliano et al., 2000). The National Institutes of Health (NIH) continues to ensure the recruitment and retention of women and members of minority groups as participants in clinical research (Public Law 103-43, 1993). The appropriate representation of women and members of minority groups in biomedical and biobehavioral research studies, especially clinical trials, remains an explicit criterion considered in the review of applications for NIH funding (Harden and McFarland, 2000).

Effective outreach to women and minorities, especially those who are difficult to access and often disenfranchised, must incorporate a partnership approach involving participation by would-be research subjects, investigators, community-based organizations, and other relevant stakeholders in the research process. Recruitment and retention of subjects in

clinical research is complex. This section complements the other sections in this Principal Investigators' Notebook and other resources available from NIH and is not meant to be a comprehensive guide. A goal of this section is to present strategies that are culturally and ethnically relevant to women and minorities and to some degree translatable across many subgroups of the U.S. population. For more tips on engaging the community and education activities, see Cancer Clinical Trials: A Resource Guide for Outreach, Education and Advocacy (*http://cancer.gov/clinicaltrials/resources/outreach-education-advocacy* or call 1-800-4-CANCER).

III BARRIERS TO RECRUITMENT AND RETENTION OF WOMEN AND MINORITIES

Limited data are available on the participation of underrepresented groups in clinical research. Lack of participation also may be exacerbated by a perceived mismatch between the cultural experiences of principal investigators and potential subjects. However, the *overall* participation rate in clinical trials also is low, ranging from 3 to 20 percent of adults (Giuliano et al., 2000; Swanson and Ward, 1995). Reasons why so few adults participate in clinical research, especially clinical trials, include:

- Fear and distrust of the research enterprise;
- Lack of knowledge;
- Lack of transportation;
- Interference with work and/or family responsibilities;
- Subject burden as a result of participation in a clinical study; and
- Financial costs.

This list is not exhaustive, but it does reflect recurring themes in the literature on this subject (NCI Cancer Clinical Trials et. al., 2001; Giuliano et al., 2001; Brown et al., 2000; Corbie-Smith et al., 1999; Shavers-Hornaday et al., 1997). Systematically addressing each of these six barriers can exert a positive effect on successful recruitment and retention of women and minorities. However, failure to address the first two barriers – lack of trust and knowledge – will absolutely undermine outreach efforts.

A *Fear and Distrust of the Research Enterprise*

From the 1940s through the late 1970s, research was widely viewed as risky to the point of death and of most value to scientists (McCarthy, 1994). Fear and distrust of the research enterprise are often associated with experiences such as the Nuremberg trial (Nuremberg Code, 1949) and the Tuskegee syphilis study (Jones, 1993). In the former, 23 Nazi scientists were prosecuted for crimes against humanity; in the latter, 400 illiterate or low-literacy African American male subjects in Alabama were

systematically denied treatment by an agency of the U.S. government for more than 30 years. An additional concern perceived by underrepresented groups is the mismatch between the cultural experiences of the PIs and potential subjects. Recent events – like the deaths of three relatively healthy volunteers in studies at The Johns Hopkins University, University of Pennsylvania, and Case Western Reserve University – have raised new concerns and remembrances of past events. The belief remains strong in minority communities that participating in a clinical trial could actually worsen one's health status or serve to stigmatize the group in which an individual holds membership (Corbie-Smith et al., 2002).

B *Lack of Knowledge*

Lack of information that is usable by individual subjects and clinicians also tends to diminish interest and participation in clinical research. Failure to inform primary health care providers may be as significant a barrier as is failure to inform participants, because even a well-informed subject may be powerless to persuade the primary health provider to refer them to clinical research studies, especially clinical trials. Another significant issue is lack of knowledge about informed consent procedures and protections. For example, some would-be research participants believe that the informed consent document protects the research institution and its staff while abridging the rights of the individual research participant.

C *Lack of Transportation*

When there is no car, and buses and taxis are difficult to access or unaffordable, the prospect of traveling to a clinical facility for research purposes may represent a formidable obstacle. For example, one would-be research participant decided that, at age 80, a bus voucher was insufficient incentive for participation when confronted with ice, snow and 34 degree temperatures. For many tribal groups in rural sections of the West and Midwest, lack of transportation may be the sole barrier to participation. Would-be research participants in underserved and rural areas require additional consideration (planning and money) to meet transportation needs.

D *Interference with Work and/or Family Responsibilities*

For many women and minority group members, work and family are closely linked – their job may be their sole link to health care, and loss of employment would mean exclusion or dropout from clinical research. Taking leave (annual or sick) to participate in research is in conflict with leave that is needed to care for an ill family member. Simple monetary incentives will not adequately address this barrier. As caregivers for dependent children, grandchildren, or aging parents, some women and minority group members clearly have no free hours left in a typical work week.

E *Subject Burden as a Result of Participation in a Clinical Study*

In the current effort to add biological/physiological/genetic variables to many studies and surveys, subjects are often burdened with repeated medical tests and trips to clinical research sites. It is incumbent on investigators to be sensitive to issues of physical pain, environmental discomforts, and the value of pleasant and encouraging staff.

F *Financial Costs*

Poverty can be a major barrier to research participation for women and men alike. Minority women and men, who tend to be overrepresented in low-income and poverty level strata, have little reserve for unpaid research costs. The cost of being away from work and family, as well as, insurance coverage or lack of coverage is a deterrent.

IV ELEMENTS OF OUTREACH

Five elements of outreach can help investigators to diminish the impact of these barriers to recruitment and facilitate success in retaining women and minorities in clinical research. These elements are, in most respects, generic principles that can be used to enhance inclusion, recruitment and retention of research subjects from most population groups. The operational details may differ when individuals are recruited in hospitals, clinics or other health care centers, rather than from the general community (such as work sites, schools, places of worship), but the underlying elements are common to all successful outreach efforts. Ideally, successful outreach would involve representatives of the population of interest in all major phases of the research process: defining the problem, developing the data collection plan, developing the recruitment and retention plan, gathering and analyzing data, disseminating the results, and developing plans to address new issues and problems. Table 1 provides an overview of these elements of outreach.

A *Element 1: Understand the Study Population*

Identify the potential research participants, the medical settings in which they are found, and the community in which they reside. This may require an assessment of racial/ethnic characteristics, socioeconomic status, age, gender, language, education/literacy levels, community structure, cultural norms and customs, migration patterns, points of access (sites of intervention), and needs and values of the potential research participants, including reasons for seeking health care.

Table 1. FIVE ELEMENTS OF OUTREACH

ELEMENT 1 *Understand the Study Population*. Learn about the people you hope to recruit. Prior beliefs may need to be changed with a goal of valuing, knowing, trusting, and understanding would-be participants. Identify the potential research participants, the medical settings in which they are found, and/or the community in which they reside. Try to learn something about their cultural norms, migration patterns and reasons for seeking health care.

ELEMENT 2 *Establish an Explicit Outreach Plan*. Establish specific goals for recruiting and retaining study participants. Where possible, involve formal and informal decision makers from local organizations and institutions, as well as the main communication channels in each medical setting or community. Establish lines of communication to promote continuing awareness of and trust in the project.

ELEMENT 3 *Achieve Agreement on Research Plans*. Confirm that the investigators, medical staff, and community all agree on the purpose for design, methodologies, implementation, and conduct of the study.

ELEMENT 4 *Design and Conduct Evaluations*. In cooperation with health care staff, community leaders and potential participants, pretest and periodically retest the recruitment and retention strategies – including resources, incentives and problem-solving mechanisms – to ensure that they conform with the needs and values of the research participants and their communities. Monitor subject accrual on a frequent and regular basis and compare results with established goals.

ELEMENT 5 *Establish and Maintain Communication*. Keeping everyone informed of progress and findings, including research staff, health care providers, participants and their families and communities. This will increase awareness of the project and demonstrate that the participants and community are valuable partners in the scientific process.

Source: *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research*, NIH Publication No. 97-4160, 1997.

1 WHY IS THIS IMPORTANT?

Working in culturally diverse settings can be challenging for even the most experienced clinical investigator. One key to success is to learn as much as possible about the groups of interest. Gathering background information about the potential study populations, their history and their communities is an essential first step, to be followed by periodic updates of this information (NHLBI, 1993a; Chen, 1993; NCI, 2001). *Note*: Investigators should observe that, while suggestions are provided in a wide range of subpopulations, the NIH Guidelines do not require that every study include every racial and ethnic group. The scientific question must determine the inclusion criteria.

Hospitals and clinics represent a special type of community and should be approached as one would any other important community. There may be differences, however. For example, research-based alcoholism after-care programs may have to compete with established hospital service programs for the same population of patients – and their personal or insurance payments. Background information on the potential study populations, especially number of potential minority and women participants, and their surroundings is also important.

a *Cultural Diversity*

Considerable heterogeneity can exist within health care settings and communities. Socioeconomic, cultural and linguistic characteristics can vary widely, along with major differences in health beliefs and practices. Recruitment and retention strategies must therefore be based on the background information about the particular groups of interest. For example, the label "Southeast Asian" does not take into consideration the major differences among Filipino, Hmong, Laotian, Vietnamese, and Cambodian peoples. The term "American Indian" is used to describe more than 550 federally recognized tribes (Parker et al., 2002). Similarly, Hispanic/Latino and African American populations have varying ethnic origins and racial characteristics and should not necessarily be considered as constituting a single subpopulation.

Country of origin, immigration status, language, and acculturation add to the wide diversity within racial and ethnic population groups, and support the need to conduct a careful assessment of the population of interest (Johnson et al., 1992; Hughes et al., 2000). Furthermore, in communities that include illegal immigrants or where illegal activities are in evidence, investigators will need special skills to evaluate the population.

b *Special Issues with Women*

The successful recruitment and retention of women in studies requires consideration of several important factors. Women of childbearing potential must understand the requirements of the study and decide whether it is appropriate for them to participate (e.g., do the benefits outweigh the risks). Even with IRB approval, the research team must make special efforts to ensure that women who are considering participation fully understand the demands of the study and what they will be asked to do. Informed consent and understanding are essential. Indeed, issues of autonomy are paramount in the decision to participate. In some instances, women may or may not wish to share their decision to participate in a study with family members or others in the community.

Other factors affect the ability of women of different ages and family statuses to participate and should be weighed when designing recruitment and retention

strategies. Child care, location of the research site, ease of access and transportation, and time away from work are only a few of these considerations.

c *Community and Population Infrastructure*

If the research study requires the inclusion of individuals in a particular geographical region, investigators must know the infrastructure and the characteristics of the health care setting, the different communities within the region, and a perspective on the region itself. Is it a rural or an urban community? What are the various cultural groups living there? In which cities or neighborhoods do each ethnic or cultural group live? What are the structure and characteristics of local health care systems and settings?

Investigators also need to gain insights about how community residents, or hospital and clinic staff, perceive the research team and its home institution. Such information is crucial in identifying potential problems and finding ways to avoid or work through them early in the outreach efforts. What is the reputation of the health services/research organization and their local partners in the community? Is there a history of responsiveness to and mutual respect for the community (state, town, region)?

2 How Do I Approach It?

Depending on the study questions and research setting, the assessment process requires different kinds of data. Several sources describe orderly assessment procedures for learning about the individuals, health care settings, and communities of interest (NCI, 1992; NHLBI, 1993b, Swanson and Ward, 1995).

a *Identify Characteristics of the Potential Participants and Setting(s)*

- *Individual characteristics:* age, sex/gender, cultural norms, education, literacy, language, health awareness, reasons for seeking medical care, knowledge of available health care services, ideas and attitudes about disease, health beliefs and practices, beliefs in effectiveness of interventions, beliefs in susceptibility of disease, access to health care, sensitivity of health care providers, religious beliefs, sexual orientation, socioeconomic level, and acculturation patterns.

- *Family characteristics*: family structure to include fictive kin (e.g., godparents and close family friends), number and age of children and other family members, number of parents and head of household, socioeconomic level, beliefs and practices, cultural norms, education, literacy, language, health awareness, and access to health care.

- *Employment characteristics*: work patterns (daytime versus night-shift work), part versus full-time employment, willingness of employers to grant leave time

for participation, and willingness of employees to take leave time for participation. How might the research process benefit employers in the community?

- *Community characteristics:* socioeconomic level, urban or rural background, migration patterns, racial and ethnic minority groups and subgroups residing in the community, health care delivery systems, civic and religious organizations, and business and community structure.

b *Identify Contacts and Points of Access that Potential Participants Might Utilize*

- *Health care decision makers:* physicians (especially referring physicians), nurses, department chairs, hospital administrators, research committees, and IRBs.
- *Community leaders:* not only political figures and government officials but also clergy, tribal leaders, teachers and principals, leaders of business and community groups, media personalities, sports figures, and youth leaders.
- *Community businesses and organizations:* schools, day-care centers, places of worship, colleges and universities including fraternities and sororities, hospitals, clinics, nursing homes, women's and men's clubs, senior and community centers, private organizations (e.g., American Heart Association and American Cancer Society), alumni associations, recreational facilities such as gyms and local recreational centers, and work sites including grocery and clothing stores, hair salons and barber shops, day spas, laundromats, banks, cleaners, restaurants, taverns, pharmacies, and fire and police stations.
- *Social service agencies:* public welfare, child welfare, tribal councils, community action agencies, public housing, community health clinics, mental health clinics, and drug treatment centers.

c *Identify Communication Channels*

- *Formal interpersonal relationships:* health care providers, religious leaders, community leaders, and school teachers.
- *Informal interpersonal relationships:* family, friends, and those who are related by language or common origins, other researchers in the hospital or clinic, former students, and other contacts.
- *Mass media:* specifically targeting women and minorities such as television, Internet including web TV, newspapers, magazines, films, and radio.

Language is a vital part of communication, and investigators from outside a particular community may not be familiar with the nuances of colloquial expressions. Another integral part of this process is a clear understanding of the *literacy levels* of participants. This literacy level must be ascertained for the

individual in her or his first language and in English. As a result, special efforts may be needed to develop and translate informational materials and other instruments so that they are sensitive to the linguistic and cultural differences among sexes/genders and members of minority groups e.g., Hispanic/Latino subpopulations and Asian subpopulations (Chen et al., 1992a,b). The National Adult Literacy Survey provides more information on minority groups and literacy (Kirsch et. al., 1993)

In general, the research staff and institution must also be aware of their own abilities and limitations in working with the diversity of participants identified for the study such as gay men and lesbians, substance abuse populations, homeless individuals, AIDS patients, older adults, and minority group members (Giachello et al., 1992).

B *Element 2: Establish an Explicit Outreach Plan*

Having determined the scientific question(s) for investigation and the study design, or in response to specific requirements of the Statement of Work in a contract solicitation, establish a specific plan, goals and objectives for recruiting and retaining study participants. Where possible, involve key community leaders, decision makers, organizations, and institutions, as well as the main communication channels in each medical setting or community. Establish lines of communication and cooperation to promote continuing awareness of and trust in the project.

1 Why Is This Important?

The development and implementation of effective recruitment and retention strategies is a multi-dimensional and evolving process. Outreach strategies that are productive in one population or setting may be counterproductive in another. For example, a door hanger announcing your research study in a middle-income, suburban neighborhood may generate little interest to casual obervers. However, in some lower-income, urban areas, a door hanger left undisturbed for several hours or days may attract undesired attention. Consequently, it is essential to involve the health care setting and/or community early in the design of outreach strategies. Hospital and/or clinic staff and community leaders and organizations are important sources of perspective on potential participants. They can provide insights into problems in study design that would otherwise become barriers to the successful accrual of participants. Forging linkages with these individuals and organizations will strengthen lines of communication, establish trust, and promote awareness (Mellins et al., 1992).

- Many members of minority groups are skeptical about participating in clinical studies. Abuses of the past are well known and have been cited by individuals as reasons for refusing to take part in a clinical study. The Tuskeegee syphilis study, for example, was a tragic deception well remembered even today. Opinion leaders such as political, religious and social leaders can become the primary link to these groups and individuals, providing key information, reassurance, and building trust.

- Leaders can inform investigators about the social and economic needs of the population. For example, the provision of basic social services has been shown to be an effective mechanism for overcoming barriers to the recruitment and retention of women and underserved populations in AIDS clinical trials in the inner cities. When payments or other incentives are offered, however, they should not be of such a magnitude as to be coercive. The level at which this occurs varies with the characteristics of the population.

- Consultation with hospital or clinic staff and formal and informal community leaders may allow investigators to "fine tune" their recruitment and retention strategies to reflect differences among individuals and groups of interest. For example, Mexicans, Puerto Ricans, Cubans, and Central or South Americans may share a common language, but they differ widely in culture and values (Shumaker et al., 1992).

2 How Do I Approach It?

The research questions will guide the development of the recruitment plan. Given the desired diversity of subjects and established sample size goals, you are encouraged to write a deliberate plan for outreach, recruitment and retention. A recruitment coordinator may be very helpful during this phase of the study (see Section D, below). The timeline also becomes a critical element in the plan. A familiar refrain in research involving minority subjects is that recruitment takes a long time; consequently it is perhaps better to err on the side of a longer recruitment period than not. Many mechanisms exist to establish explicit goals for appropriate recruitment and retention; several suggestions are presented here:

- Identify recruitment and retention goals as specifically and explicitly as possible, with the collaboration of a statistician, hospital or clinic staff and community leaders.

- Involve hospital staff and/or community leaders early in the process. For example, present the study plans to the community leaders, physicians and others in the health care settings. The plan may be presented to the broader community on neutral territory such as a local school in a minority community. Consider creating a diverse advisory board comprised of racial/ethnic and sex/gender representation such as study staff, health care providers, where warranted, community members, and participants. Incentives should be considered for community members who would be advisory board members.

- Include one or more representative(s) from the research institution, hospital or clinic staff as members of the research team to serve as liaisons between the researchers, the staff and the participants. Ideally, a staff member residing in the community of interest would serve a meaningful role as liaison.

- Offer hospital or clinic staff and/or community organizations opportunities to participate at different levels of involvement, from establishing and taking part in focus groups, to providing sponsorship for the study, to assisting in recruiting, to contributing to the writing or reviewing of proposals. A useful practice to follow is that for every scientific paper or report written there is a corresponding version for the interested lay community.

- Recruit women and minority investigators and health care staff for the project. Racial/ethnic and sex/gender equivalence among staff and participants may enrich goals for appropriate recruitment and retention. Consider subcontracting specific components of the research activities to hospital or clinic staff and/or community organizations that are well known. Consortium arrangements with research institutions and hospitals with an established history of serving the underrepresented groups would be useful in increasing recruitment in clinical research.

C *Element 3: Achieve Agreement on Research Plans*

Confirm that the investigators, medical and health care staff, and/or community all agree on the purpose of design, methodologies, implementation, and conduct of the study.

1 Why Is This Important?

Women and minorities must be included in clinical research if scientists are to make valid inferences about health and disease in these groups. It is essential that investigators strive to build the level of understanding and trust that will lead to a productive partnership and successful conduct of the research project.

2 How Do I Approach It?

Many mechanisms exist to achieve agreement; several are presented here:

- Consult the hospital or clinic staff and/or the community at every stage of the study. It is much easier to achieve agreement on issues if all parties have been involved from the earliest stages. Mutually beneficial collaboration can be achieved and maintained for many years, if the hospitals', clinics' and communities' needs, concerns and recommendations are taken into account. Involve the hospital or clinic staff and/or community in the planning, as well as the conduct of the research. Understanding and responding to individual and group concerns can lead to more appropriate and useful results. Women and minority groups are likely to appreciate and trust investigators with demonstrated collaborative skills. This process may require substantial time.

- Present the proposed study, complete with rationale and plans for implementing it, to those who are expected to recruit subjects or answer public questions. This can be accomplished through announcements in public forums, hospital and community newsletters and special mailings. Do not use jargon in describing the proposed research.
- Create a diverse advisory board that includes key members of hospital or clinic staff and community organizations. This can be a very effective mechanism for establishing and maintaining a functional study. Not only can an advisory board guide sensitive and sensible recruitment, it can also assist in understanding and reenlisting those who drop out of the study.
- Identify ways of including and rewarding hospital or clinic staff so that they find the research satisfying and interesting.
- On an on-going basis, ask diverse advisory boards to review the research plans to ensure that incentives are appropriate for the community, no undue coercion is used, and materials are appropriate in terms of language and literacy levels.

D *Element 4: Design and Conduct Evaluations*

Design and implement an evaluation plan to assess how well the recruitment and retention strategies are working. In cooperation with community leaders, health care staff and potential participants, investigators should pretest and periodically retest the recruitment and retention strategies – including resources, incentives and problem-solving mechanisms – to ensure that they conform with the needs and values of the research participants and their communities. Monitor subject accrual on a frequent and regular basis and compare results with established goals.

Study design should include a process for systematically documenting the extent to which recruitment and retention objectives were accomplished during a defined period of time for a defined population. Such an evaluation will help investigators to (1) determine which strategies work well; (2) certify the degree of progress that has occurred; and (3) identify elements that are not working.

1 Why Is This Important?

Evaluation is an integral part of developing and planning the recruitment and retention strategies (NCI, 1992, 2001). As such, evaluation provides investigators with tools for the following tasks:

- Addressing the issues of feasibility: (Can the goals be accomplished with the existing staff and resources within the time frame specified?);
- Addressing the issues of accountability to the research institutions, research participants and their families, and the community;
- Providing information to encourage the acceptance and response of the community and research participants involved; and
- Providing a feedback mechanism to guide changes in current strategies to avoid or counter participant drop out.

2 How Do I Approach It?

Depending upon the type of evaluation being conducted, important elements form the basis for evaluation. Investigators wishing to learn more about any of the different types of evaluation are urged to seek guidance from an expert or consult the literature on this subject (Frechtling and Sharp, 1997). Because this can be a complex process, only the most general elements are presented here.

a *Establish Evaluation Measures*

- *Study staff*: time-line schedules, work performed, and response to participants over time.
- *Media outreach*: publicity, promotion, type and extent of media coverage, estimated audience size and demographics, and materials planned and distributed.
- *Population response*: volume of inquiries, screening participation rates, and interviewees' perceptions of screening and proposed study and staff.
- *Enrollment rates*: proportion of eligible subjects who agree to participate.
- *Continuing functions and response*: number of phone calls or meetings with community-based organizations, advisory boards, focus groups, and other patient or participant groups.
- *Compliance*: participants' continuing responses to study protocols and demands.
- *Feedback*: consultation with and responses from research participants, community leaders, and hospital or clinic staff.

b *Use Evaluation Data to Refine the Recruitment and Retention Strategies*

- Are some of the objectives not being met? Why?
- Are there strategies or activities that are not succeeding? Why?
- Are more resources required, or can resources be used more efficiently?
- What are the strengths and weaknesses of the strategies or mechanisms for retaining study participants?

c *Establish an Ongoing, Problem-Solving Mechanism*

This mechanism should include not only regularly scheduled meetings with participant focus groups and hospital or clinic staff involved in the study, but also adequate mechanisms for tracking patients and investigating each patient withdrawal to determine if some aspect of the retention strategy is at fault. Investigators may also need to provide counseling to address the social needs that can impede the participation of women and members of minority groups in a clinical study (e.g., child care, transportation costs, study site location, availability of parking). Above all, investigators must remain flexible within the constraints of the study goals and objectives.

d *Pretest and Retest*

Before initiating the full-scale project, investigators typically find it useful to conduct a pilot test of the proposed recruitment and retention strategies. This will allow the opportunity to test the feasibility of the planned approach and amend it according to feedback from the study population. Potential participants can contribute valuable information on the needs, cultures and values of the population of interest and the community in which they reside. It is during this preliminary test period that the investigator can best determine the most cost-effective distribution of resources, including materials, equipment, personnel, and time. Based on this information, fiscal and budgetary planning can be finalized and problem-solving mechanisms can be put in place (Rand et al., 1992).

Pilot testing can also provide feedback on proposed strategies and incentives, such as educational materials, hiring staff from the proposed study population, establishing a project office in the community, providing transportation, and other compensations (e.g., meals, food coupons, child care, or cash). Problem-solving mechanisms instituted following the pilot study can include regularly scheduled reviews to identify barriers that are interfering with compliance or continued participation.

Periodic retesting and refining of recruitment and retention strategies can also be important, for the following reasons:

- Resources can vary during the course of the study, so it may be prudent to identify alternative mechanisms in advance. Should problems arise, local agencies or organizations may serve as back-ups. By the same token, members of the research team may need to take over some of the recruitment functions if they prove too time-consuming for hospital or clinic staff.
- Community leaders and hospital or clinic staff can assist in determining the most appropriate distribution of resources – for example, instances where volunteers may be used in lieu of paid staff and the availability of bilingual and sign interpreters.

E *Element 5: Establish and Maintain Communication*

Establish mechanisms for keeping all those involved in the study (research staff, health care providers, participants and their families and communities) apprised of progress and, ultimately, study findings. This will not only increase understanding and awareness of the project, but will recognize the participants and their health care setting or community as valuable partners in the scientific process.

1 Why Is This Important?

Effective communication of study results is another important element in building trust in the community. Researchers must remember, however, that their professional priorities may conflict with the priorities of study participants. Specifically, publication of research results in scientific journals has little value to participants and could be perceived as exploitive unless the same results are also conveyed to the participants, and their communities, in a sensitive manner (Shumaker et al., 1992). Providing the community and the hospital or clinic staff with a detailed report on the progress of research is often the first step in developing a long-term relationship of trust and cooperation. Future relationships with these populations could depend on whether they perceive their role as that of partners in the research or merely "guinea pigs."

Communication of study results should therefore be among the ethical considerations of any research project (see below). Dissemination of research findings can also promote awareness of social, medical and educational resources that have been made available as a result of the project.

2 How Do I Approach It?

Educated consumers of research may be more likely to participate in research. Research institutions must do more to educate those who will be targeted as potential research participants. The following avenues of communication can be used not only for

announcing the study and recruiting participants, but also for disseminating study results (Rand et al., 1992). The important point is that participants, their health care providers, and their communities understand the outcome of the study and that their inestimable contribution is noted and appreciated.

a *Use Formal Communication*

Formal methods of communication involve the media, including radio (e.g., talk shows, ethnic language stations, and public service announcements), print (such as flyers, posters, hospital newsletters, and newspaper articles in language appropriate to the proposed study group), and television (e.g., talk shows, news shows, cable access channels, and ethnic language stations).

b *Use Informal Communication*

Informal methods of communication can include personal contact (e.g., telephone, door-to-door, neighborhood events, schools, staff meetings) and multiple sites of contact (e.g., health clinics, social service agencies, hospitals and clinics, places of worship, union halls, senior citizen centers, shelters, grocery stores, beauty salons, day care centers, and support groups).

c *Establish Feedback Mechanism*

Feedback mechanisms can and should be utilized in the participants' language to ensure ongoing success and retention of participants and that follow-up questionnaires reach participants. Study results should also be provided at the completion of the study, along with the appreciation of the principal investigator and staff.

d *Hire an Outreach Coordinator*

Consider employing an outreach coordinator, whose responsibilities might include:

- Setting up monthly meetings with health care or community-based organizations and developing linkages to enhance research participation and to "trouble-shoot" problems;
- Developing and preparing health care or community-oriented educational materials;
- Attending health care or participant meetings, community health fairs or block parties to periodically disseminate study information;
- Providing requested information about the research study to individuals and health care and/or community groups through educational presentations and workshops;
- Providing in-service training and guidance to all investigative staff, to ensure that they are sensitive to the needs, attitudes, and concerns of study participants;

- Providing education and training to health care and/or community leaders to ensure that they understand the benefits and demands of research and the role participants and their health care setting and/or communities play in such collaboration;
- Convening periodic meetings of scientific staff and health care and/or community leaders (or advisory board) to assess retention and to devise strategies for countering drop out and bolstering retention and protocol adherence; and/or
- Addressing participants' questions of, "What is in it for me?" The coordinator might emphasize health services and benefits accorded subjects in clinical research such as routine physical examinations, comprehensive medical screening, free and/or reduced cost medications and laboratory services.

e *Announce Study Results*

At the conclusion of the study, the research team may wish to host a special presentation for participants, hospital or clinic staff, and community groups to discuss the outcome of the study and its subsequent application to health.

V SUCCESSFUL STRATEGIES

Numerous reports suggest that, despite Federal policies and guidelines, the customary research subject is still a white male. Many investigators still fail to routinely include women and minorities in their study populations. In some cases, stereotyped as "difficult to reach," "noncompliant," "unreliable," and "unwilling," women and minorities have not been routinely included in trials, or trialists have systematically excluded them. At the same time, historical, educational, cultural, linguistic, economic, geographic, and social barriers have caused many would-be participants to be fearful, unwilling, and/or unable to participate in clinical research studies (Millon Underwood, 2000; Corbie-Smith, 1999; Hayunga and Pinn, 1996; Millon Underwood et al., 1993). The following success stories are derived from efforts by NIH to be inclusive. Tips and tools for successful recruitment and retention strategies are presented.

A *Study of Women's Health Across the Nation (SWAN)*

Funded initially in September 1994, SWAN is supported by the National Institute on Aging, the National Institute of Nursing Research, the National Heart, Lung and Blood Institute, Office of Research on Women's Health, the National Institute of Mental Health, and the National Center for Complementary and Alternative Medicine. A variety of methods were used to recruit a sample of multi-ethnic women (Sowers et al., 2000). A total of 202,985 households or telephone numbers were

Table 2. STRATEGIES FOR RECRUITING AND RETAINING WOMEN AND MINORITIES IN CLINICAL RESEARCH[1]

Involve the Community

- Develop community networks including a community advisory group to facilitate community entry.
- Minority-based Greek organizations may be helpful in gaining entry and trust of the community. Principal investigators may wish to contact the local chapter of the: Alpha Kappa Alpha sorority, Delta Sigma Theta sorority, Alpha Phi Alpha fraternity, Omega Psi Pi fraternity, and others.
- Solicit the support, participation and if appropriate collaboration of women and minority community physicians who provide care for the desired population groups.
- Solicit the support and participation of ministers and ministerial alliance groups in recruiting and retaining study participants.
- Develop promotional and educational materials designed to increase awareness in the community.
- Solicit the support of health care decision makers, community leaders, businesses, social service agencies, and organizations.
- Identify communication channels that are culturally sensitive and language appropriate.

Involve the Participants

- Include women and minority participants in designing the research and preparing study materials to be sure they meet their needs and expectations and are culturally and linguistically sensitive.
- Messages of altruism that convey the benefits of the research for future generations (e.g., "for your daughter's sake") or staying healthy in order to be there for the family (e.g., "families need their fathers") received positive responses from women and minorities.
- Create a participant advisory board to give feedback on forms used, recruitment activities, study procedures, etc.
- Recruit participants to plan social events and coordinate daily tasks associated with running a clinical research investigation.

Staff Your Team Right

- Women and minority investigators and educators can often foster greater trust among female and minority participants.
- Include women and members of minority groups on your research staff, particularly women and minorities with the same ethnic or racial background as the target population. This strategy may not provide immunity to problems of distrust and fear but should lessen the severity of the problem.
- All staff should be instructed to ask how the participant would like to be addressed (Mr., Mrs. first name or nickname). The participant's response should be noted in the research record. Staff turnover may mandate that this step be repeated. Address older adults more formally than younger participants.
- Provide pictures of staff in the research setting and include staff pictures in newsletters to facilitate identity and relationships among staff and participants.

Address Logistical and Financial Needs

- Maintain extended and flexible clinic hours. Weekend work may be required.
- Provide at-home or work site follow-up for participants.
- Attempt to combine protocol visits with existing medical appointments.
- Offer childcare and transportation – or reimburse patients for these services.
- Offer parents small gifts for their children. This may serve as an additional incentive and acknowledges parents' sacrifices and absence from childcare responsibilities.
- Reimburse patients for their time. Financial incentives may range from $5.00 up to as much as $25.00 per visit. Gift certificates and large cash lotteries may be popular with some groups. Obviously, cultural and religious norms should be observed.
- Explore potential of insurance coverage for ancillary care and other expenses associated with participation.
- For each research participant, maintain a list of alternate contacts to improve your options for staying in touch since some women and minority groups may be highly mobile.

Improve Communication

- Provide additional time and assistance to those participants with special needs, e.g., parents with young children, older adults, persons with hearing and sight limitations, those with low literacy levels and participants for whom English is a second language, since they may require extra efforts to understand what is required of them.
- Allow extra time to review the study's benefits and limits with options for 1:1 exchange of information. Videotaped messages may be helpful in low literacy groups. Remember, some minority groups regard research as guinea pig experimentation so the extra time will allow for questions and answers. Some women may be momentarily distracted by other competing demands such as children, "to do" lists, or other physical needs. Extra time under these circumstances may allow for refocusing.
- Study materials should be tailored with consideration of cultural and demographic characteristics of women or minority group(s).
- Pictorial representation or use of videotape media might be used to explain the research.
- Inform participants of tangible benefits such as free or reduced cost services associated with participation in clinical research.
- Inform the participant's own health care provider about study progress, results and outcomes.
- Inform participants about the study protocol, treatment, and implications through meetings, research teas, newsletters, health fairs or other regular updates.
- Acknowledge the contributions of patients in ways that are meaningful to them such as certificates of appreciation, cards on birthdays or other special occasions, invitation to join "lay" speakers bureau or other public recognition.
- Use focus groups to identify and understand potential barriers to participation of women and minority group members.

Source: Adapted from the NIDA Clinical Trials Network brochure "Successfully Including Women in Clinical Trials."

screened for women eligible for participation in the SWAN Cross-Sectional Study, and 16,065 women were eligible and completed the interview. Of these, 6,521 women were cohort-eligible and asked to participate in the SWAN Longitudinal Study; a total of 3,306 women entered the Longitudinal Study.

Each of seven sites surveyed one of four minority populations and a Caucasian population. Each site employed community development and outreach strategies to engage community gatekeepers. These gatekeepers included ministerial alliance groups who were apprised of the planned study and were requested to give support to the study by informing their congregations. Some of the sites used flyers and doorknob literature packets as a way of preparing the communities. The investigators also used newsletters, with staff pictures, to keep the community and participants informed of study progress.

Recruitment incentives included diagnostic testing (with results sent to the women's health providers), a small freezer (used to retain samples) that became the women's property to keep at the conclusion of the study, and community health fairs. Note cards, birthday cards and other printed forms of communication were employed in the study to acknowledge the value of participants to the study.

B *Mental Health Services for Women in Public Medical Care*

Investigators conducted a research project focused on women seen in county-run healthcare settings serving poor young women (primarily WIC Clinics and Family Planning Clinics) in Prince George's and Montgomery counties, MD, and Arlington County, VA. Previous studies have documented that untreated mental disorders in primary care settings represent a serious public health problem. However, these studies did not include young poor women (a group at high risk for these mental disorders, yet low mental health users), who rarely are seen in primary health care settings.

Prior to beginning the National Institute of Mental Health-funded project, researchers spent one year courting providers in county clinics, including the WIC program, family planning clinics and pediatrics, in order to gain access to the population of interest. Researchers worked to establish relationships and trust with the clinics by providing services and consultation and by working at integrating themselves into the clinic team (e.g., attending regular clinic meetings and providing services that went beyond mental health services such as child care, and translation services).

Significant resources were invested in pursuing subjects. These included repeated phone outreach and face-to-face contacts at home or work or during regular primary care clinic appointments. Investigators were careful not to become intrusive: the decision to pursue subjects was based on reports from the women that the repeated attempts to reach them signaled caring on the part of the researcher. The significance

of racial and ethnic match between provider and subject was unclear, but outreach and trust issues were significant issues. Often women were not immediately responsive, but would later agree to enter care. Through outreach efforts, they realized they could trust the study staff and would turn to them when crises in their lives occurred.

Data collection for this study ends in 2003. The researchers are pilot testing community-based interventions, such as partnering with an ongoing "Promotoras de Salud" program (a lay health worker program funded by the Daughters of Charity), to examine the feasibility of such organizations providing outreach and support services to supplement traditional mental health care services for disadvantaged minorities with mental health care needs.

C *African American Hereditary Prostate Cancer (AAHPC) Study*

This multicenter genetic linkage study was organized by Howard University and the National Human Genome Research Institute, with support from the National Center on Minority Health and Health Disparities and the National Cancer Institute. Six Collaborative Recruitment Centers were responsible for the identification and enrollment of 100 African American families; recruitment strategies included mass media campaigns, physician referrals, community health fairs/prostate cancer screenings, support groups, tumor registries, as well as visits to churches, barber shops, and universities.

Investigators utilized various incentives depending on the site, including a copy of the subject's family tree, plaques with inscriptions related to the study, free medical screening, and reimbursement for travel and other related expenses. The study was publicized through presentations at professional meetings and other physician organizations and groups. Some strategies did not work as well as anticipated, including flyers and presentations at churches and racial/ethnic specific groups, health fairs and cancer screening events (Royal, 2000). By far, the most productive recruitment mechanisms were physician referrals and tumor registries.

VI CONCLUSION

Data on successful recruitment and retention strategies for women and minorities in clinical research suggests that strategies tailored to the inclusion, recruitment and retention of a specific study, with deliberate consideration for the target population, is critical to its success. Recurring barriers in clinical research (fear and distrust, lack of knowledge, lack of transportation, interference with work and family, intense subject burden, and financial costs) are modifiable. Further, the flexibility and readiness of staff to modify or add elements of outreach may be helpful in improving accrual of women and minorities in clinical studies.

Section 5

Human Subjects Protections and Inclusion Issues

Human Subjects Protections and Inclusion Issues

Ethical issues involved in the conduct of biomedical research are a topic of considerable debate. Clinical trials in particular will remain a focal point, given the nature and scope of the expanding need for clinical research and existing global public health concerns such as AIDS, cancer, gene therapy, diseases related to aging, resistant bacteria, and biological warfare. Well-publicized failures in the conduct of clinical research have left some groups suspicious of the motives and methods of medical research. As informed and knowledgeable research practitioners, we can begin by making sure that medical research practices are sound and ethical.

As indicated above, concerns about clinical researchers and the research environment have led to debates about the best way to promote high standards in research and the ethical conduct of research. A greater transparency of the process, in concert with open communication is essential to restore the public's faith in clinical research. Researchers have an obligation to participants and to the research endeavor to ensure that the design and conduct of studies are both sound and ethical. Elements of the ethics of research on human subjects are provided below.

WHAT ARE THE ETHICAL PRINCIPALS THAT GOVERN RESEARCH INVOLVING HUMAN SUBJECTS

The *Public Health Service Act* requires that each entity which applies for a grant, contract or cooperative agreement for any project or program which involves the conduct of biomedical or behavioral research involving human subjects provide evidence that the research plan protects the rights and welfare of human subjects by minimizing risks, selecting subjects equitably, obtaining informed consent, and ensuring privacy and confidentiality and has established an Institutional Review Board (IRB) to review the research project.

The *Code of Federal Regulations*, Title 45, Part 46 Protection of Human Subjects (45 CFR 46), Subpart A is the federal policy for the protection of human subjects, and is referred to as "The Common Rule." The Common Rule implements the sections of the Public Health Service Act relevant to the Protection of Human Research Subjects. (The analogous FDA regulations, 21 CFR 50 and 56 have similar requirements.)

The regulations are implemented by the IRB.

The *Belmont Report* (a report of the National Commission for the Protection of Human Subjects) attempts to summarize the basic ethical principles for the conduct of biomedical and behavioral research involving human subjects. Three basic principles encompassed in the *Belmont Report* are:

1 *Respect for Persons* – treating individuals as autonomous agents and ensuring protection of persons with diminished autonomy.

2 *Beneficence* – securing the well being of persons by doing no harm and maximizing possible benefits and minimizing possible harms.

3 *Justice* – fairness in the distribution of benefits and burdens among research subjects.

Implementation of Belmont Principles

The key feature of ethical research is consent to participation. Consent safeguards a subject's autonomy. An individual maintains control over their life by deciding either to consent or not to consent. Additionally, consent protects human dignity. The individual is recognized as having inherent worth, and may not be used as mere means to an end. Furthermore, consent provides assurance, to the public, that researchers are not manipulating or deceiving human subjects. Finally, consent elevates subjects of research to be participants in research, and to realize that their participation is essential to the research process.

The fair selection of research subjects is critical to the ethical conduct of research. Fair selection ensures that no single population is approached too often for participation or is placed at increased risk because circumstance makes them unable to refuse to participate in research. Conversely, fair selection means that no single population is selected to receive only the benefits of research while never having been asked to assume any potential harms associated with participating in research.

A *Informed Consent*

Human subjects in research must participate willingly. Voluntary participation also means that subjects have enough information to give informed consent (consent of participation provided by the participant with full knowledge of the risks and benefits). The signed informed consent document must include information on the purpose and benefit of the research, all foreseeable risks or discomforts, study duration, research contact person, right to withdraw, and whether the research is classified.

The informed consent documents should be clear, concise, informative, and explained in a manner that is understood by the research participant. Informed consent, whether oral or written, may not include language that appears to waive the subject's legal rights or that appears to release the investigator or anyone else from liability for negligence.

Investigator(s) and staff(s) should take precautionary measures to ensure that ethical concerns are clearly noted in the informed consent document, to minimize the possibility of coercion or undue influence in the incentives or rewards offered in recruiting into or retaining participants in studies.

For example, some minority groups may fear lack of sensitivity and objectivity by the research team about their needs, values and beliefs, or if they will receive the same level of care as other groups in the study. For this reason, the informed consent process should include one or more information sessions about the goals of the research and the reasons for differences in participation between groups, if they exist.

Developing an informed consent document that meets the needs of diverse groups may require an understanding of health problems and conditions of different racial and ethnic subpopulations, as well as attention to socioeconomic differences involving occupation, income, education, religious beliefs, and cultural values.

B *Conflict of Interest*

Although conflicts of interest are not restricted to clinical research, unmanaged conflicts of interest in the context of clinical research have had the appearance of leading to bad consequences and have led to lingering mistrust of clinical researchers.

IRB Review of Protocols and Approval of Consent Documents
(*http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finguid.htm*)

All IRBs (Institutionally based and non-Institutionally based) should be cognizant of the source of funding and funding arrangement for each protocol they review, and the source and arrangement for the funding the IRB's review of each protocol.

When an institutional official or conflict of interest committee or its equivalent determines that a potential Institutional conflict is problematic, the IRB should review the Institution's financial relationship to the sponsor of a specific trial and determine whether the trial should be permitted to be carried out at the Institution. If so, the IRB should consider how this should best be managed, including what modifications might need to be made to the protocol or to the Consent form.

When the institutional official or conflict of interest committee or equivalent determines that a clinical investigator has potential conflict of interest that cannot be eliminated, and must be reduced or managed in some way, IRBs should consider not only what modifications might need to be made to the protocol or Consent, but also other approaches as appropriate.

IRBs should carefully consider the specific mechanisms proposed to minimize the potential adverse consequences of the conflict in an effort to optimally protect the interests of the research subjects. In general, if there are any financial conflict of interest issues on the part of the clinical investigator, he or she should not be directly engaged in aspects of the trial that could be influenced inappropriately by that conflict. These could include: the design of the trial, monitoring the trial, obtaining the informed consent, adverse event reporting, or analyzing the data.

II DATA AND SAFETY MONITORING PLAN AND DSMBS

NIH policy requires that investigators submit a general description of the data and safety monitoring plan for clinical trials (biomedical and behavioral intervention studies) as part of the research application. In developing your Data and Safety Monitoring Plan, you should refer to the NIH Policy for Data and Safety Monitoring (*http://grants.nih.gov/grants/guide/noticefiles/NOT-OD-00-038.html.* See also (*http://grants.nih.gov/grants/guide/notice-files/not98-084.html*).

NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants.

A DSMB is an independent research monitoring board. Generally, experts in all scientific disciplines needed to interpret the data and ensure patient safety should conduct the monitoring activities. Ideally, participants in monitoring a trial are in no way associated with the trial. Committee membership can include clinical trial experts, biostatisticians, bioethicists, or other clinicians.

The objectives of the DSMB are to ensure (1) risks associated with participation are minimized to the extent practical, (2) integrity of the data, and (2) ethics of the clinical trial. Additionally the DSMB has the responsibility to stop a trial if safety concerns arise or if the objectives of the trial are met.

All clinical trials, including physiologic, toxicity, and dose-finding studies (Phase I); efficacy studies (Phase II); and efficacy, effectiveness and comparative trials (Phase III) will require monitoring if the studies have multiple clinical sites, are blinded (masked), or if they include high-risk interventions or vulnerable populations. (See *http://grants.nih.gov/grants/guide/notice-files/not98.084.html*).

The method and degree of monitoring needed is related to the degree of risk involved to the participants as well as size, complexity, and scope of the research effort. The monitoring effort can range from monitoring by the principal investigator or the NIH program staff in a small Phase I study to the establishment of an independent DSMB for a large trial.

III INSTITUTIONAL REVIEW BOARD (IRB)

As IRBs implement current guidelines for the inclusion of women and minorities and their subpopulations, they must also implement the regulations for the protection of human subjects as described in 45 CFR 46, "Protection of Human Subjects." They should also take into account the Food and Drug Administration's (FDA's) "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," Vol. 58 Federal Register 39406.

A *What Is the Role of the IRB?*

An IRB is a group that has been formally designated to review and monitor biomedical and behavioral research involving human subjects in accordance with DHHS and/or FDA regulations. An IRB has the authority to approve, require modification in, or disapprove research to ensure protection for human's subjects.

IRBs that approve studies of products regulated by the FDA must be in compliance with 21 CFR 50 & 56. Federal funds support does not need to be involved for the FDA regulations to apply. However, when research studies involving products regulated by FDA are funded and supported by DHHS, the research institution must comply with both the DHHS (45 CFR 46) and FDA (21 CFR 50&56) regulations.

The IRB must prospectively review and approve any changes that occur in your human subject research procedures. If unanticipated problems occur, or if human subjects are harmed, including physical injury, or there is improper disclosure of private information, economic loss or other harmful occurrences, the IRB must be notified.

IRBs are also responsible for determining whether informed consent is required from the subjects involved and secure whether privacy and confidentiality protections are adequate.

When appropriate, the IRB should also determine that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects, to protect the privacy of subjects, and to maintain the confidentiality of the data.

Institutions engaged in human subject research must ensure that the composition of the IRB membership and its position within the institution's administrative structure provides the IRB with the freedom to make decisions and conduct its oversight activities in an autonomous manner.

Broad participation by members outside the institution, who have no interest in the outcome of the research and the business interests of the institution, is encouraged as a way of protecting the integrity of the IRB process.

B *What Are the Criteria for IRB Approval of Research?*

The essential criteria for IRB approval of research are based on the ethical principals that govern your research as outlined in the Belmont Report. The following requirements must be met in order to have your research reviewed and approved by the IRB:

- Risks to subjects must be minimized;
- Risks to subjects must be reasonable in relation to anticipated benefits;
- Selection of subjects must be equitable;
- Informed consent must be sought from each prospective subject or the subjects legally authorized representative; and
- The research plan must be appropriately monitored to ensure the privacy of subject data, the safety of subjects, and protection of their rights and welfare, particularly for vulnerable populations.

From time to time, changes are made in the human subjects regulations and in their interpretation by IRBs and by the Office of Human Research Protections and the Center for Scientific Research. It is important to review and understand thoroughly the most current regulations before starting research.

In all cases, good judgment, openness of the recruitment and retention process and reliance upon objective, third party oversight can effectively minimize the potential for harm to subjects and safeguard the integrity of the research.

Section 6

Appendices

Appendix A

Glossary

Acculturation: Degree to which people from a particular cultural or ethnic group display behavior that reflects the influence of pervasive, mainstream norms of behavior.

Assimilation: Extent to which an individual enters a new culture and becomes a part of it. Includes both the motivation of the individual to enter the mainstream culture and the extent to which members of the mainstream culture welcome or discourage the entry and inclusion of that person in the mainstream culture.

Clinical research: The definition of clinical research for the purposes of the NIH policy on the inclusion of women and minorities in clinical studies was amended in 2000 to reflect the accepted definition from the 1997 Report of the NIH Director's Panel on Clinical Research which can be found at the following URL: *http://www.nih.gov/news/crp/97report/execsum.htm.* The Panel recommended that the NIH use the following definition as its standard for all analyses. Clinical research was defined in three parts as follows:

1 Patient-oriented research. 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 and/or obtains readily identifiable private information. Excluded from this definition 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.

3 Outcomes research and health services research.

Clinical trial (NIH-defined Phase III): NIH has developed a special definition for an NIH-defined Phase III clinical trial to be used regarding this policy when referring to a clinical trial. This is to distinguish this type of trial from the other types of clinical research which NIH supports, and from other definitions, e.g. by the Food and Drug Administration (FDA).

For the purpose of the NIH policy, an NIH-defined Phase III clinical trial is a broadly based prospective Phase III 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.

In determining whether a study fits the NIH definition of a Phase III clinical trial, an essential consideration is trial outcome - whether it would contribute to a change in the standard of care or contribute to a change in public health policy, regardless of the number of participants in the study. This NIH definition of a Phase III clinical trial is broad and encompases the wide range of research that NIH sponsors. It **differs** from the **FDA definition of Phase III clinical trials**, which focuses primarily on a clinical investigation of drugs, vaccines, biologics, and devices. Clinical trials of experimental drugs covered in the FDA definition proceed through four phases (21 CFR Section 312.21, 4/1/94 edition). For additional information regarding the FDA definitions of the different phases of clinical trials, check the NIH Clinical Trials Website at: *http://clinical trials.gov*.

Community-based organizations: Organizations that have their origins or basis within the community and which utilize some aspect of the community's goals, mandate, or objectives as part of their efforts.

Communication channels: The means by which a message gets from a source to a receiver. Mass media channels are more effective in making people aware of a new idea; interpersonal channels are more effective in persuading people to adopt a new idea.

Cultural competence: A set of academic and interpersonal skills that allows individuals to increase their understanding and appreciation of cultural differences and similarities within, among, and between groups. This requires a willingness and ability to draw on community-based values, traditions, and customs and to work with persons who are knowledgeable about and from the community in developing focused interventions, communications, and other supports.

Cultural diversity: Differences in race, ethnicity, language, nationality, or religion among various groups within a community, organization, or nation. A city is said to be culturally diverse if its residents include members of different racial and/or ethnic groups.

Cultural sensitivity: Respect for ethnic individuals and for their culture; the recognition that such individuals have cultural health beliefs and practices; the integration of those beliefs and practices in the overall treatment plan for the patient.

Ethnicity: easily identifiable characteristic that implies a common cultural history with others possessing the same characteristic. Based on Federal reporting standards the ethnic categories required by NIH are Hispanic/Latino or not Hispanic/Latino. Hispanic/Latino includes persons of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

Formative evaluation: Collects information about the components of the recruitment and retention aspects of the research project. Information from this type of evaluation can be used to test messages, select communications channels, and revise the communication process.

Health disparities: Diseases, disorders, and conditions that disproportionately afflict individuals who are members of racial and ethnic minority groups.

Health literacy: the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decision.

Health promotion: is the combination of educational and environmental supports for actions and conditions of living conducive to health.

Impact evaluation: Focuses on the long-range results of the program and subsequent changes in health status. Impact evaluations are rarely possible because they are costly, involve extended commitment, and may depend upon other strategies in addition to the recruitment and retention component of the research project.

Majority group: Typically used to describe a group of individuals, self-identified as white, not of Hispanic Origin, and referring to a person or persons having origins in any of the original peoples of Europe, North Africa, or the Middle East.

Minority groups: A minority group is a readily identifiable subset of the U.S. population that is distinguished by racial, ethnic, and/or cultural heritage. The following racial/ethnic minority groups are those currently identified by the Office of Management and Budget (OMB) for federal reporting: American Indian/Alaska Native; Asian, Black or African American, Hispanic/Latino, Native Hawaiian or Other Pacific Islander. The minority group (and subpopulation) to which an individual belongs is determined by self-reporting. This classification is for administrative purposes and is prevalent in the scientific and other literature and databases available for research. The purpose of investigators routinely specify the racial/ethnic population(s) under investigation is to systematically obtain data on the various minority groups and subpopulations. Related goals are to fill the gaps of health research information for these populations, and to reduce/eliminate health disparities and to ensure results are applicable to all citizens. Investigators may report their findings in the research literature consistent with the purpose of the research.

Multicultural: Designed for, or pertaining to, two or more distinctive cultures.

Outcome evaluation: Provides descriptive information on the project and can be used to document short-term results. Task-focused results describe the output of the activities (i.e., number of participants recruited as a result of a talk show in a local television station). Short-term results describe the immediate effects of the strategies on the target population (i.e., percentage of the target group that is participating in one of the research protocols).

Outreach strategies: These are outreach efforts by investigators and their staff to appropriately recruit and retain populations of interest into research studies. Such efforts should represent a thoughtful and culturally sensitive plan of outreach and generally include involvement of other individuals and organizations relevant to the populations and communities of interest, e.g., family, religious organizations, community leaders and informal gatekeepers, and public and private institutions and organizations. The objective is to establish appropriate lines of communication and cooperation to build mutual trust and cooperation such that both the study and the participants benefit from the collaboration.

Process evaluation: Documents the degree of implementation of the recruitment and retention activities. It describes how many items, of what materials, are provided to whom, by whom, and when and whether they responded. This type of evaluation may look at the origin of the research project, the methods used, the target population, program personnel/staff, and cost.

Sex/Gender: The term gender refers to the classification of research subjects into either or both of two categories: women and men. Sex refers to biological sex, either male or female. *For inclusion purposes, biological sex should be used, either male or female.*

Significant difference: For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

Site of intervention: A specific location used to establish contact with or gain access to subjects within the neighborhood or community in which they reside. Examples include schools, work sites, beauty shops, barber shops, ethnic grocery stores, small group meetings in people's homes, community clinics, hospitals, and day-care centers.

Subpopulations: Each racial/ethnic group contains subpopulations which are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting.

Underserved: individuals or groups who lack access to health services or health-related information relative to the national average. The underserved population may include residents of rural, remote or inner-city areas; members of certain racial and ethnic groups; socioeconomically disadvantaged persons; or people with disabilities.

Valid analysis: The term "valid analysis" 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 of the question of interest are:

- allocation of study participants of both sexes/genders (males and females) and from 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 gender and racial/ethnic groups.

Appendix B

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Appendix C

NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended October 2001

Summary: This notice updates the NIH policy on the inclusion of women and minorities as subjects in clinical research. It supercedes the 1994 Federal Register notice (*http://grants.nih.gov/grants/guide/notice-files/not94-100.html*) and the August 2000 notice in the NIH Guide to Grants and Contracts (*http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html*). It incorporates the definition of clinical research as reported in the 1997 Report of the NIH Director's Panel on Clinical research. Also, this notice provides additional guidance on reporting analyses of sex/gender and racial/ethnic differences in intervention effects for NIH-defined Phase III clinical trials. The guidelines ensure that all NIH-funded clinical research will be carried out in a manner sufficient to elicit information about individuals of both sexes/genders and diverse racial and ethnic groups and, particularly in NIH-defined Phase III clinical trials, to examine differential effects on such groups. Since a primary aim of research is to provide scientific evidence leading to a change in health policy or standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently.

In June 2001, NIH adopted the definition of clinical research as: (1) Patient-oriented research. 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 this definition 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; and (3) Outcomes research and health services research *http://www.nih.gov/news/crp/97report/execsum.htm.*

Effective Date: This amended policy is effective immediately and applies to all grants and cooperative agreements currently active and to be awarded. Contract solicitations issued as of October 2001 must adhere to the amended policy.

Note: 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.*

LEGISLATIVE BACKGROUND

The NIH Revitalization Act of 1993, PL 103-43, signed into law on June 10, 1993, directed the NIH to establish guidelines for inclusion of women and minorities in clinical research.

The statute states that:

> In conducting or supporting clinical research for the purposes of this title, the Director of NIH shall ... ensure that (a) women are included as subjects in each project of such research; and (b) members of minority groups are included in such research. 492B(a)(1)

The statute further directed the NIH to establish guidelines to specify:

a. the circumstances under which the inclusion of women and minorities as subjects in projects of clinical research is inappropriate …;

b. the manner in which clinical trials are required to be designed and carried out …; and

c. the operation of outreach programs … 492B(d)(1)

The statute defines "clinical research" to include "clinical trials" and states that:

> In the case of any clinical trial in which women or members of minority groups will be included as subjects, the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial. 492B(c)

Specifically addressing the issue of minority groups, the statute states that:

> The term "minority group" includes subpopulations of minority groups. The Director of NIH shall, through the guidelines established...define the terms "minority group" and "subpopulation" for the purposes of the preceding sentence. 492B(g)(2)

The statute speaks specifically to outreach and states that:

> The Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in the projects of clinical research. 492B(a)(2)

The statute includes a specific provision pertaining to the cost of clinical research and, in particular clinical trials.

A i In the case of a clinical trial, the guidelines shall provide that the costs of such inclusion in the trial is (sic) not a permissible consideration in determining whether such inclusion is inappropriate. 492B(d)(2)

ii In the case of other projects of clinical research, the guidelines shall provide that the costs of such inclusion in the project is (sic) not a permissible consideration in determining whether such inclusion is inappropriate unless the data regarding women or members of minority groups, respectively, that would be obtained in such project (in the event that such inclusion were required) have been or are being obtained through other means that provide data of comparable quality. 492B(d)(2)

Exceptions to the requirement for inclusion of women and minorities are stated in the statute, as follows:

> The requirements established regarding women and members of minority groups shall not apply to the project of clinical research if the inclusion, as subjects in the project, of women and members of minority groups, respectively –
>
> 1 is inappropriate with respect to the health of the subjects;
>
> 2 is inappropriate with respect to the purpose of the research; or
>
> 3 is inappropriate under such other circumstances as the Director of NIH may designate. 492B(b)

B In the case of a clinical trial, the guidelines may provide that such inclusion in the trial is not required if there is substantial scientific data demonstrating that there is no significant difference between-

i the effects that the variables to be studied in the trial have on women or members of minority groups, respectively; and

ii the effects that the variables have on the individuals who would serve as subjects in the trial in the event that such inclusion were not required. 492B(d)(2)

II POLICY

A *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, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. 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. This policy applies to research subjects of all ages in all NIH-supported clinical research studies.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design or contract proposal appropriate to the scientific objectives of the study/contract. The research plan/proposal 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 such subjects. Such a plan/proposal should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

B *NIH-defined Phase III Clinical Trials: Planning, Conducting, and Reporting of Analyses for Sex/Gender and Race/Ethnicity Differences.*

When an NIH-defined Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important sex/gender and race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

Investigators must consider the following when planning, conducting, analyzing, and reporting an NIH-Defined Phase III clinical trial. Based on prior studies, one of the three situations below will apply:

1 Prior Studies Support the Existence of Significant Differences

If the data from prior studies strongly support the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, the primary question(s) to

be addressed by the proposed NIH-defined Phase III clinical trial and the design of that trial must specifically accommodate this. For example, if men and women are thought to respond differently to an intervention, then the Phase III clinical trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.

The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct analyses to detect significant differences in intervention effect (see DEFINITIONS - Significant Difference) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable. The final protocol(s) approved by the Institutional Review Board (IRB) must include these plans for analysis. The award will require that for each funded protocol, investigators must report in their annual Progress Report cumulative subject accrual and progress in conducting analyses for sex/gender and race/ethnicity differences. If final analyses of sex/gender and race/ethnicity are not available at the time of the Final Progress Report or Competing Continuation for the grant, a justification and plan ensuring completion and reporting of the analyses are required. If final analyses are required as part of the contract, these analyses must be included as part of the deliverables. These requirements will be cited in the terms and conditions of all awards for grants, cooperative agreements and contracts supporting NIH-defined Phase III clinical trials.

Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

2 Prior Studies Support No Significant Differences

If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic and/or relevant subpopulation comparisons, then sex/gender and race/ethnicity will not be required as subject selection criteria. However, the inclusion and analysis of sex/gender and/or racial/ethnic subgroups is still strongly encouraged.

3 Prior Studies Neither Support nor Negate Significant Differences

If the data from prior studies neither strongly support nor strongly negate the existence of significant differences of clinical or public health importance in intervention effect based on sex/gender, racial/ethnic, and relevant subpopulation comparisons, then the NIH-defined Phase III clinical trial will be required to include sufficient and appropriate entry of sex/gender and racial/ethnic participants, so that valid analysis of the intervention effects can be performed. However, the trial will not be required to provide high statistical power for these comparisons.

The Research Plan (for grant applications) or Proposal (for contract solicitations) must include a description of plans to conduct valid analysis (see DEFINITIONS - Valid Analysis) by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable. The final protocol(s) approved by the Institutional Review Board (IRB) must include these plans for analysis. The award will require that for each funded protocol, investigators must report in their annual Progress Report cumulative subject accrual and progress in conducting analyses for sex/gender and race/ethnicity differences. If final analyses of sex/gender and race/ethnicity are not available at the time of the Final Progress Report or Competing Continuation for the grant, a justification and plan ensuring completion and reporting of the analyses are required. If final analyses are required as part of the contract, these analyses must be included as part of the deliverables. These requirements will be cited in the terms and conditions of all awards for grants, cooperative agreements and contracts supporting NIH-defined Phase III clinical trials.

Inclusion of the results of sex/gender, race/ethnicity and relevant subpopulations analyses is strongly encouraged in all publication submissions. If these analyses reveal no differences, a brief statement to that effect, indicating the groups and/or subgroups analyzed, will suffice.

For all three situations, cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

III ROLES AND RESPONSIBILITIES

While this policy applies to all applicants/offerors for NIH-supported clinical research, certain individuals and groups have special roles and responsibilities with regard to its implementation.

1 NIH Staff

The NIH staff provide educational opportunities for the extramural and intramural communities concerning this policy; monitor its implementation during the development, review, award and conduct of research; and manage the NIH research portfolio to comply with the policy.

2 Principal Investigators

Principal investigators should assess the theoretical and/or scientific linkages between sex/gender, race/ethnicity, and their topic of study. Following this assessment, the principal investigator and the applicant/offeror institution will address the policy in each application and proposal, providing the required information on inclusion of women and minorities and their subpopulations in clinical research projects, and any required justifications for exceptions to the policy.

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 United States. If there is scientific rationale for examining subpopulation group differences within the foreign population, investigators should consider designing their studies to accommodate these differences.

Investigators and their staff(s) are urged to develop appropriate and culturally sensitive outreach programs and activities commensurate with the goals of the study or objectives of the contract. The objective should be to actively recruit and retain the most diverse study population consistent with the purposes of the research project. Indeed, the purpose should be to establish a relationship between the investigator(s) and staff(s) and populations and community(ies) of interest such that mutual benefit is derived for participants in the study. Investigator(s) should take precautionary measures to ensure that ethical issues are considered, such that there is minimal possibility of coercion or undue influence in the incentives or rewards offered in recruiting into or retaining participants in studies.

To assist investigators and potential study participants, NIH staff have prepared educational materials, including a notebook titled, "NIH Outreach Notebook on the Inclusion of Women and Minorities in Biomedical and Behavioral Research." The notebook, as well as the Frequently Asked Questions document, are located at the following URL: *http://grants.nih.gov/grants/funding/women_min/women_min.htm*

3 Institutional Review Boards (IRBs)

It is the responsibility of the IRBs to address the ethical issues as outlined in Section IV(2) for Principal Investigators. As the IRBs implement the regulation for the protection of human subjects as described in Title 45 CFR Part 46, "Protection of Human Subjects", *http://ohrp.osophs.dhhs.gov/human subjects/guidance/45cfr46.htm* they must also attend to the guidelines for the inclusion of women and minorities and their subpopulations in clinical research. They should take into account the Food and Drug Administration's "Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," Vol. 58 *Federal Register* 39406 *http://www.fda.gov/cder/guidance/old036fn.pdf*.

4 Peer Review Groups

In conducting peer review for scientific and technical merit, appropriately constituted initial review groups (including study sections), technical evaluation groups, and intramural review panels are instructed, as follows:

- to evaluate the proposed plan for the inclusion of minorities and both genders for appropriate representation or to evaluate the proposed justification when representation is limited or absent,

- to evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects,
- to evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the purpose of the research,
- to determine whether the design of clinical trials is adequate to measure differences when warranted,
- to evaluate the plans for valid analysis for NIH-defined Phase III clinical trials,
- to evaluate the plans for recruitment/outreach for study participants, and
- to include these criteria as part of the scientific assessment and evaluation.

The review instructions for grants are available on line at the following URL: *http://grants.nih.gov/grants/peer/hs_review_inst.pdf*

For contracts, the contracting officer will provide instructions for contract reviewers. Further information on instructions for contracts may be obtained at the following URL: *http://oa.od.nih.gov/oamp/index.html.*

Or contact:

National Institutes of Health
Division of Acquisition Policy and Evaluation
Office of Acquisition Management and Policy
6100 Executive Boulevard, Room 6C01
Phone: 301-496-6014
Fax: 301-402-1199

5 NIH Advisory Councils

In addition to other responsibilities for review of projects where the peer review groups have raised questions about the appropriate inclusion of women and minorities, the Advisory Council/Board of each Institute/Center shall prepare biennial reports, for inclusion in the overall NIH Director's biennial report, describing the manner in which the Institute/Center has complied with the provisions of the statute.

6 Institute/Center Directors

Institute/Center Directors and their staff shall ensure compliance with the policy.

7 NIH Director

The NIH Director may approve, on a case-by-case basis, the exclusion of projects, as recommended by the Institute/Center Director, that may be inappropriate to include within the requirements of these guidelines on the basis of circumstances other than the health of the subjects, the purpose of the research, or costs.

IV DEFINITIONS

Throughout the section of the statute pertaining to the inclusion of women and minorities, terms are used which require definition for the purpose of implementing these guidelines. These terms, drawn directly from the statute, are defined below.

A *Clinical Research*

Clinical research is defined as:

(1) Patient-oriented research. 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 this definition 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,
(3) Outcomes research and health
services research. *http://www.nih.gov/news/crp/97report/execsum.htm*

B *NIH-defined Clinical Trial*

For the purpose of these guidelines, an NIH-defined "clinical trial" is a broadly based prospective Phase III 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.

C *Valid Analysis*

The term "valid analysis" 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 of the question of interest are:

- allocation of study participants of both sexes/genders (males and females) 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.

D *Significant Difference*

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

E *Racial and Ethnic Categories*

1 Minority Groups

A minority group is a readily identifiable subset of the U.S. population that is distinguished by racial, ethnic, and/or cultural heritage.

The Office of Management and Budget (OMB) Directive No. 15 *http://www.whitehouse.gov/omb/fedreg/ombdir15.html* defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The categories in this classification are social-political constructs and should not be interpreted as anthropological in nature.

When an investigator is planning data collection on race and ethnicity, these categories shall be used. The collection of greater detail is encouraged. However, more detailed items should be designed in a way that they can be aggregated into these required categories. Using respondent self-report or self-identification to collect an individual's data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation. Respondents shall be offered the opportunity to select more than one racial designation. When data are collected separately, provision shall be made to report the number of respondents in each racial category who are Hispanic or Latino.

The following definitions apply for ethnic categories.

- *Hispanic or Latino* – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
- *Not Hispanic or Latino*

The following definitions apply for racial categories.

- *American Indian or Alaska Native* – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- *Asian* – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (*Note*: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- *Black or African American* – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
- *Native Hawaiian or Other Pacific Islander* – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

2 Majority Group

- *White* – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

NIH recognizes the diversity of the U.S. population and that changing demographics are reflected in the changing racial and ethnic composition of the population. The terms "minority groups" and "minority subpopulations" are meant to be inclusive, rather than exclusive, of differing racial and ethnic categories.

3 SUBPOPULATIONS

Each racial and ethnic group contains subpopulations that are delimited by geographic origins, national origins and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race or ethnicity. Researchers should be cognizant of the possibility that these racial/ethnic combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study.

F *Outreach Strategies*

These are outreach efforts by investigators and their staff(s) to appropriately recruit and retain populations of interest into research studies. Such efforts should represent a thoughtful and culturally sensitive plan of outreach and generally include involvement of other individuals and organizations relevant to the populations and communities of interest, e.g., family, religious organizations, community leaders and informal gatekeepers, and public and private institutions and organizations. The objective is to establish appropriate lines of communication and cooperation to build mutual trust and cooperation such that both the study and the participants benefit from such collaboration.

V NIH CONTACTS FOR MORE INFORMATION

The following senior extramural staff from the NIH Institutes and Centers may be contacted for further information about the policy and relevant Institute/Center programs:

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Appendix D

NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research

Release Date: August 8, 2001
Notice: NOT-OD-01-053
National Institutes of Health

Policy: The NIH has adopted the 1997 Office of Management and Budget (OMB) revised minimum standards for maintaining, collecting, and presenting data on race and ethnicity for all grant applications, contract and intramural proposals and for all active research grants, cooperative agreements, contract and intramural projects. The minimum standards are described in the 1997 OMB Directive 15, *http://www.whitehouse.gov/OMB/fedreg/ombdir15.html.*

Summary: This document provides additional guidance and instruction for using the revised minimum standards for maintaining, collecting, and presenting data on race and ethnicity found in the PHS 398 (rev. 5/01) and PHS 2590 (rev.5/01) instructions and forms *http://grants.nih.gov/grants/forms.htm*. Comparable information will be provided in research and development contract solicitations and awards for intramural projects. This document should be used in conjunction with the instructions in the PHS 398 and PHS 2590 instructions and forms.

The 1997 OMB revised minimum standards include two ethnic categories (Hispanic or Latino, and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. Using self-reporting or self-identification to collect an individual's data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation.

Collection of this information and use of these categories is required for research that meets the NIH definition of clinical research.

Effective Date: This policy applies to all new applications and proposals, annual progress reports, competing continuation applications, competing supplement applications for research grants, contracts, and intramural projects as of January 10, 2002.

REVISED MINIMUM STANDARDS FOR MAINTAINING, COLLECTING, AND PRESENTING FEDERAL DATA ON RACE AND ETHNICITY

The following are the ethnic and racial definitions for the minimum standard categories (1997 OMB Directive 15).

Ethnic Categories

- *Hispanic or Latino* – A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
- *Not Hispanic or Latino*

Racial Categories

- *American Indian or Alaska Native* – A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
- *Asian*: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (*Note*: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- *Black or African American* – A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
- *Native Hawaiian or Other Pacific Islander* – A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- *White* – A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Using respondent self-report or self-identification to collect an individual's data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation.

When reporting these data in the aggregate, investigators should report: (a) the number of respondents in each ethnic category; (b) the number of respondents who selected only one category for each of the five racial categories; (c) the total number of respondents who selected multiple racial categories reported as the "number selecting more than

one race"; and, (d) the number of respondents in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed items should be designed in a way that they can be aggregated into the required categories for reporting purposes. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. Federal agencies will not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

II GUIDANCE ON REPORTING ETHNICITY/RACE AND SEX/GENDER IN CLINICAL RESEARCH

NIH requires all grants, contracts, and intramural projects conducting clinical research to address the Inclusion of Women and Minorities (see *http://grants.nih.gov/grants/funding/women_min/women_min.htm*). NIH defines clinical research as: (1) Patient-oriented research. 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 this definition 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, or (d) development of new technologies. (2) Epidemiologic and behavioral studies. (3) Outcomes research and health services research.

A *New Applications (type 1), Competing Continuations (type 2), Requests for Proposals, and Intramural Projects*

1 Submitting Applications or Proposals Involving the Collection of New/Additional Data in Clinical Research:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender. This information must be reported using the newly revised categories and according to the new format provided in the Targeted/Planned Enrollment table *http://grants.nih.gov/grants/funding/phs398/enrollment.pdf*

2 Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories. If the existing data on ethnicity and race

allows accurate correspondence with the new categories, the investigator can use the format in the Targeted/Planned Enrollment table. However, if the existing data do not allow accurate correspondence with the new categories, information may be reported using the former categories and according to the format in the 4/98 Version of the Inclusion Table *http://grants.nih.gov/grants/funding/women_min/Inclusion Old_Form.pdf*

3 Annual Progress Reports (type 5) and Competing Supplement Applications

In Annual Progress Reports and Competing Supplement Applications, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date (as well as any proposed additions to the Targeted/Planned enrollment in the case of Competing Supplement Applications) and to present the distribution by ethnic/racial categories and sex/gender.

4 If Data Collection is Ongoing, Such that New Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators may choose to report ethnicity/race and sex/gender sample composition using EITHER the format in the former 4/98 Version of the Inclusion Table OR the new Inclusion Enrollment Report *http://grants.nih.gov/grants/funding/phs398/enrollment report.pdf* [*Note*: If investigators with on-going data collection choose to report information using the new Inclusion Enrollment Report, they must continue to use this format for the remaining years of the project.]

5 If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators may EITHER continue to report using the former categories and according to the 4/98 Version of the Inclusion Table, OR, if data allow accurate correspondence with the new categories, use the format in the new Inclusion Enrollment Report.

III FREQUENTLY ASKED QUESTIONS

1 What categories should I use in my application to estimate race and ethnicity, given the new OMB standards?

Investigators should use the categories described in the PHS 398 instructions and listed in the table "Targeted/Planned Enrollment Table" for New Applications. First, the investigator should report the anticipated total number of males and females to be enrolled by Ethnicity (Hispanic or Latino, Not Hispanic or Latino). Then, the investigator should report the anticipated total number of males and females by Racial Categories (American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White). The total number of subjects in the Ethnic Category section of the table should equal the total number of subjects in the Racial Categories section. Investigators do not need to estimate

the anticipated number of individuals reporting multiple racial categories (either total number reporting multiple categories or number reporting specific combinations) for New Applications. However, the investigator must follow the OMB guidelines, which include allowing respondents to select multiple race categories, once data collection commences.

2 What if my new application involves analyzing secondary data in which the race and ethnicity categories do not comply with the new OMB guidelines?

If an investigator is using secondary data sets that do not conform to the new OMB guidelines and does not plan to collect any new/additional data from the subjects, this should be noted in the New Application. In this circumstance, the investigator should complete the "Targeted/Planned Enrollment Table" for a New Application and the "Inclusion Enrollment Report" for Continuation Applications, Competing Supplement Applications, and Annual Grant Progress Reports if the data allow. However, if the existing data do not allow accurate correspondence with the new categories, the investigator should report the information using the prior categories and use the 4/98 Version of the Inclusion Table.

3 There are many ways of tabulating the multiple race and ethnicity responses, particularly since the race and ethnicity categories are not mutually exclusive. Do the numbers I report have to "add up"?

The numbers in several parts of the two tables must be the same. In both the "Targeted/Planned Enrollment Table" for a New Application and the "Inclusion Enrollment Report" for Continuation Applications, Competing Supplement Applications, and Annual Progress Reports, the sum in "Ethnic Category: Total of All Subjects" must equal the sum in "Racial Categories: Total of All Subjects." In addition, the "Racial Categories: Total Hispanics or Latinos" in Part B of the "Inclusion Enrollment Report Table" must equal the Total Hispanic or Latino number reported in Part A of the "Inclusion Enrollment Report." Footnotes in the tables clearly identify which numbers must be the same.

4 Can I use the Targeted/Planned Enrollment Table or the Enrollment Inclusion Report to collect data from individuals?

Neither the Targeted/Planned Enrollment Tablet nor the Enrollment Inclusion Report should be used for collecting data from individuals. These tables are only to be used for reporting aggregate data.

To collect data from an individual respondent, investigators should use respondent self-report or self-identification and use two separate questions. The first question should be about ethnicity, followed by a question that provides the option of selecting

one or more racial designations. An example of a format for collecting information from an individual can be found in the "Ethnic Origin and Race" section of the Personal Data Form Page in the PHS 398 (rev. 5/01) *http://grants.nih.gov/grants/funding/phs398/personal.pdf*

5 Can I ask more detailed questions about ethnicity and race than these guidelines indicate?

The revised OMB guidelines provide minimal standards for data collection. Indeed, researchers are encouraged to explore collecting additional types of information on race and ethnicity that will provide additional insights into the relationships between race and ethnicity and health. For example, after asking the ethnicity and then the race questions, researchers may opt to ask study participants who choose multiple categories to identify the group that they identify with primarily. Further questions identifying membership in subpopulations within the ethnic and racial categories provided by OMB may also be considered. The scientific question being addressed in the study should guide investigators' decisions regarding collection of any additional information on ethnicity or race. Information on subpopulations may be reported by listing the information in an attachment to the required table.

6 I have already begun data collection and my categories do not comply with the new OMB standards. Do I need to change my questions on race and ethnicity in the middle of the study?

If data collection has already begun, we do not expect investigators to change their questions on race and ethnicity prior to the completion of the study. For Annual Progress Reports, in this circumstance, investigators should note that the research project was initiated prior to the implementation of the new reporting guidelines. If the data do not accurately correspond with the new categories, the investigator may continue to use the format in the 4/98 Version of the Inclusion Table.

7 I began data collection prior to the new standards, but my race and ethnicity questions comply with the new standards. I submitted my original estimates of the study composition using the old standards. How should I present the data in the progress report?

If you began your data collection prior to the implementation of the new standards but your questions on race and ethnicity comply with the new standards, the choice is left up to the investigator as to how to present the data for Annual Progress Reports. We suggest completion of the new Inclusion Enrollment Report.

8 How should I report race and ethnicity data when my research involves a foreign population?

Investigators are encouraged to design their data collection instruments in ways that allow respondent self-identification of their racial and ethnic affiliation.

However, these items should be designed in a way that they can be aggregated into the required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables, investigators should asterisk and footnote the table indicating that data includes foreign participants. If the aggregated data only includes foreign participants, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign participants, we suggest the investigator complete two separate tables BB one for domestic data and one for foreign data, with an asterisk and footnote accompanying the table with foreign data.

9 How do the 1997 OMB revised standards differ from the previous standards?

OMB issued the previous standards for maintaining, collecting, and presenting data on race and ethnicity in 1977. The minimum acceptable categories were: American Indian or Alaska Native; Asian or Pacific Islander; Black, not of Hispanic origin; Hispanic; White, not of Hispanic origin.

The 1997 OMB revised standards now include two ethnic categories (Hispanic or Latino or Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). When using self-reporting or self-identification to collect data on ethnicity and race, investigators should use two separate questions with ethnicity information collected first followed by the option to select more than one racial designation.

Additional Information and NIH Contacts Additional information on NIH policy regarding the Inclusion of Women and Minorities in Clinical Research can be found at the website *http://grants.nih.gov/grants/funding/women_min/women_min.htm*.

The following senior extramural staff from the NIH Institutes and Centers may be contacted for further information about the policy and relevant Institute/Center programs:

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Appendix E

Grants, Old Inclusion Table, Targeted/Planned Enrollment Table, Inclusion Enrollment Table, Contracts, Inclusion Enrollment Program Annual Technical Progress Report

Inclusion Table

This report should NOT be used for data collections from study participants.

Principal Investigator/Project Director_____
(Last, First, Middle)

Grant Number (if known):_____

Study Title:_____

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, Not of Hispanic Origin	Hispanic	White, Not of Hispanic Origin	Other or Unknown	Total
Female							
Male							
Unknown							
Total							

Sample Form

Targeted/Planned Enrollment Table

This report should NOT be used for data collections from study participants.

Study Title:_____

Total Planned Enrollment:_____

Targeted/Planned Enrollment: Number of Subjects			
	Sex/Gender		
Ethnic Category	*Females*	*Males*	*Total*
Hispanic or Latino			
Not Hispanic or Latino			
Ethnic Category Total of All Subjects*			
Racial Categories			
American Indian/Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
Racial Categories: Total of All Subjects*			

**The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."*

Inclusion Enrollment Report Table

This report should NOT be used for data collections from study participants.

Study Title:_____

Total Enrollment:_____ Protocol Number:_____

Contract Number:_____

PART A: *Total Enrollment Report*: Number of Subjects Enrolled to Data (Cumulative) by Ethnicity and Race				
	Sex/Gender			
Ethnic Category	*Females*	*Males*	*Unknown or Not reported*	*Total*
Hispanic or Latino				**
Not Hispanic or Latino				
Unknown (Individuals not reporting ethnicity)				
Ethnic Category Total of All Subjects*				*
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or not reported				
Racial Categories: Total of All Subjects*				*

PART B: *Hispanic Enrollment Report*: Number of Hispanics or Latinos Enrolled to Date (Cumulative)				
Racial Category	*Females*	*Males*	*Unknown or Not reported*	*Total*
American Indian/Alaska Native				
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or not reported				
Racial Categories: Total of Hispanics and Latinos				**

**These totals must agree*
***These totals must agree*

Inclusion Enrollment Report: Contracts

This report should NOT be used for data collections from study participants.

Study Title:_____

Total Enrollment:_____ Protocol Number:_____

Contract Number:_____

PART A: *Total Enrollment Report*: Number of Subjects Enrolled to Data (Cumulative) by Ethnicity and Race				
	Sex/Gender			
Ethnic Category	*Females*	*Males*	*Unknown or Not reported*	*Total*
Hispanic or Latino				
Not Hispanic or Latino				
Unknown (Individuals not reporting ethnicity)				
Ethnic Category Total of All Subjects*				
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or not reported				
Racial Categories: Total of All Subjects*				
PART B: *Hispanic Enrollment Report*: Number of Hispanics or Latinos Enrolled to Date (Cumulative)				
Racial Category	*Females*	*Males*	*Unknown or Not reported*	*Total*
American Indian/Alaska Native				
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or not reported				
Racial Categories: Total of Hispanics and Latinos**				

**These totals must agree*

***These totals must agree*

Use when the contract involves human subjects *unless* it has been determined by the government that the inclusion of women & minority groups in the study population is *not* appropriate.

Annual Technical Progress Report Format for Each Study: Contracts

Study Title:_____

Date:_____

Provide the number of subjects enrolled in the study to date according to the following categories:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, Not of Hispanic Origin	Hispanic	White, Not of Hispanic Origin	Other or Unknown	Total
Female							
Male							
Unknown							
Total							

Subpopulations of the minority groups should also be repoted using a similar format.

Use for follow-on or renewal contracts involving human subjects that began collecting data *prior* to FY02 *only* if the data being collected does not fit into the 10/2001 standards (see Inclusion Enrollment Report) *Note: Whenever possible and appropriate, the "Inclusion Enrollment Report" should be used in lieu of this reporting format.*

Appendix F

Resources Available on the Internet

I OER INCLUSION OF WOMEN AND MINORITIES POLICY IMPLEMENTATION

http://grants.nih.gov/grants/fundng/women_min/women_min.htm
Provides links to:

- **A** October 2001 Amended Policy on Inclusion of Women and Minorities as Subjects in Clinical Research
- **B** August 2001 Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research
- **C** Old and New Enrollment Tables for reporting Target and Enrollment Data

II ORWH POLICY ON WOMEN'S INCLUSION AS PARTICIPANTS IN RESEARCH

http://www4.od.nih.gov/orwh/inclusion.html
Provides links to:

- **A** NIH-wide aggregate Inclusion data Reports prepared by the NIH Tracking and Inclusion Committee;
- **B** Outreach Notebook that includes a Question and Answer section to assist in the preparation of research applications and in the development of outreach activities as they relate to the inclusion of women and minorities as subjects in clinical research.

III OER PEER REVIEW POLICY AND ISSUES

http://grants.nih.gov/grants/peer/peer.htm
Provides information about Review policies, in particular reviewer instructions for evaluating inclusion of women and minorities in clinical research and analysis plans for NIH Phase-III Clinical Trials.

IV NIH FORMS AND APPLICATIONS

http://grants.nih.gov/grants/forms.htm
Provides links to the PHS 398 and PHS 2590 Instructions and Forms.

http://rcb-intranet.nci.nih.gov/
Provides links to RFP and Contract Workforms.

Appendix G

45 CFR 46

Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Source: *Federal Register*, November 13, 2001 (Volume 66, Number 219), Rules and Regulations, Page 56775-56780, from the Federal Register Online via GPO Access [wais.access.gpo.gov] [DOCID:fr13no01-9].

§46.201 TO WHAT DO THESE REGULATIONS APPLY?

a Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

b The exemptions at Sec. 46.101(b)(1) through (6) are applicable to this subpart.

c The provisions of Sec. 46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in Sec. 46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

d The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 DEFINITIONS

The definitions in Sec. 46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

a Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

b Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

c Fetus means the product of conception from implantation until delivery.

d Neonate means a newborn.

e Nonviable neonate means a neonate after delivery that, although living, is not viable.

f Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

g Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

h Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§46.203 DUTIES OF IRBS IN CONNECTION WITH RESEARCH INVOLVING PREGNANT WOMEN, FETUSES, AND NEONATES.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§46.204 RESEARCH INVOLVING PREGNANT WOMEN OR FETUSES.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

a Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

b The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

c Any risk is the least possible for achieving the objectives of the research;

d If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

e If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

f Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

g For children as defined in Sec. 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

h No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

i Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

j Individuals engaged in the research will have no part in determining the viability of a neonate

§46.205 RESEARCH INVOLVING NEONATES.

a Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

1 Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2 Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3 Individuals engaged in the research will have no part in determining the viability of a neonate.

4 The requirements of paragraph (b) or (c) of this section have been met as applicable.

b Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

1 The IRB determines that:

i The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

ii The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

2 The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

c Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

1 Vital functions of the neonate will not be artificially maintained;

2 The research will not terminate the heartbeat or respiration of the neonate;

3 There will be no added risk to the neonate resulting from the research;

4 The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

5 The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

d Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 RESEARCH INVOLVING, AFTER DELIVERY, THE PLACENTA, THE DEAD FETUS OR FETAL MATERIAL.

a Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

b If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 RESEARCH NOT OTHERWISE APPROVABLE WHICH PRESENTS AN OPPORTUNITY TO UNDERSTAND, PREVENT, OR ALLEVIATE A SERIOUS PROBLEM AFFECTING THE HEALTH OR WELFARE OF PREGNANT WOMEN, FETUSES, OR NEONATES.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.204 or Sec. 46.205 only if:

a The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

b The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the *Federal Register*, has determined either:

1 That the research in fact satisfies the conditions of Sec. 46.204, as applicable; or

2 The following:

i The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

ii The research will be conducted in accord with sound ethical principles; and

iii Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

APPENDIX H

POWERPOINT SLIDE SHOW

SEX/GENDER AND MINORITY INCLUSION IN NIH CLINICAL RESEARCH: WHAT INVESTIGATORS NEED TO KNOW

Sex/Gender and Minority Inclusion in NIH Clinical Research

What Investigators Need to Know!

1

Overview

- Review and Rationale of Policy
- Recent Up-Dates & Implications
  - Definition of Clinical Research
  - OMB Standards
  - NIH-Defined Phase III Trials
- Resources and Getting Help

2

NIH Policy on Inclusion of Women & Minorities in Clinical Research

- Why does NIH have this policy?
  - Mandated by Congress, 1993 PL 103-43
  - Ethical principal of justice and importance of balancing research burdens and benefits

3

Public Law PL 103-43

- Women and Minorities must be included in all clinical research studies
- Women and Minorities must be included in Phase III clinical trials in numbers adequate for valid analysis
- Cost is NOT allowed as an acceptable reason for exclusion
- NIH to support outreach efforts to recruit and retain women, minorities, and their subpopulations in clinical studies

4

NIH Policy on Inclusion

- NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended October, 2001
- http://grants1.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

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Updates to Inclusion Policy

- NIH Definition of Clinical Research
- New OMB Standards for Data on Ethnicity and Race
- Further Clarification about NIH-Defined Phase III Clinical Trials

6

NIH Definition of Clinical Research

(1) Patient-oriented research.

- 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 this definition 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;

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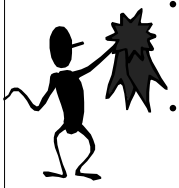
NIH Definition of Clinical Research (continued)

(2) Epidemiologic and behavioral studies;

(3) Outcomes research and health services research.

8

Instructions in PHS 398



- **Best source of information for investigators**
- **http://grants1.nih.gov/grants/funding/phs398/phs398.html**

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Instructions in PHS 398

- **Section E: Human Subjects Research**
  - **Inclusion of Women**
  - **Inclusion of Minorities**
- **Failure to include = Return Application Prior to Review**

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Instructions in PHS 398

- **Inclusion of Women and Minorities Sections must include:**
  - **Subject Selection Criteria & Rationale**
  - **Rationale for Any Exclusions**
  - **Enrollment dates (start and end)**
  - **Outreach Plans for Recruitment**
  - **Proposed Composition Using New Tables**

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Reviewer Instructions

- **Reviewers evaluate the Inclusion Plans**

http://grants1/nih.gov/grants/peer/hs_review_inst.pdf

- **Unacceptable plans must be reflected in the priority score**

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Funding Decisions

- **Applications with Unacceptable Plans cannot be funded – must revise plans!**

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Update to NIH Policy for Inclusion

- **New OMB Standards**
- **OMB Directive 15 Issued 1997**
  - **Racial and Ethnic Standards for Federal Statistics and Administrative Reporting**
  - **Effective Date No Later Than January 1, 2003**

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Update to NIH Policy for Inclusion

- **OMB Directive 15 Issued 1997**
  - **Collecting Data by Self-Report:**
  - **Two Separate Questions**
    - Question 1: A sk about Ethnicity
    - Question 2: Ask about Race WITH OPTION to select more than one racial designation

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NIH Policy for Inclusion

- OMB Directive 15 Issued 1997
  - Ethnic Categories:
    - Hispanic or Latino
    - Not Hispanic or Latino
  - Racial Categories:
    - American Indian or Alaska Native
    - Asian
    - Black or African American
    - Native Hawaiian or Other Pacific Islander
    - White

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Personal Data Form PHS 398: Examples

ETHNICITY

1. Do you consider yourself to be Hispanic or Latino? (See definition below.) Select one.

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

☐ Hispanic or Latino

☐ Not Hispanic or Latino

RACE

2. What race do you consider yourself to be? Select one or more of the following.

☐ American Indian or Alaska Native. A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

☐ Asian. A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

☐ Black or African American. A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black" or African American."

☐ Native Hawaiian or Other Pacific Islander. A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

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

☐ Check here if you do not wish to provide some or all of the above information.

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Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title:

Total Planned Enrollment:

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino			
Not Hispanic or Latino			
Ethnic Category Total of All Subjects*			
Racial Categories			
American Indian/Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
Racial Categories: Total of All Subjects*			

The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects.

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Update to NIH Inclusion Policy

- **NIH-Defined Phase III Clinical Trials**
  - **Evidence must be reviewed to show whether clinically important sex/gender and race/ethnicity differences in intervention effect are expected**
  - **Plans for valid analysis must be included in the design**
  - **Results of analyses must be reported to NIH**

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Requirements for NIH-Defined Phase III Clinical Trials

- **Research plan must include one of the following:**
  - Prior studies support significant differences between subgroups:
  - Need plans to conduct valid analyses to detect significant differences between sex/gender and/or racial/ethnic subgroup s
    - For the purpose of this policy, Significant Difference is defined as a difference that is of clinical or public health importance based on substantial scientific data. This is not the same as "statistically significant difference. "

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Requirements for NIH-Defined Phase III Clinical Trial Applications

OR:

- **Prior studies support no significant differences between subgroups:**
  - **Representation as subject selection criterion is not required; however, inclusion and analyses are encouraged**

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Requirements for NIH-Defined Phase III Clinical Trial Applications

OR:

- Prior studies neither support nor negate significant differences in intervention effect between subgroups:
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (Does not require high statistical power)
  - **For the purpose of this policy, Valid Analysis means an unbiased assessment that does not require high statistical power and should be conducted for both large and small studies.**

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Reviewer Instructions for Phase III Clinical Trials

- **Reviewers evaluate inclusion AND analysis plans**

http://grants1/nih.gov/grants/peer/hs_review_inst.pd f

- **Unacceptable plans must be reflected in the priority score**

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Funding Decisions for Phase III Clinical Trials

- **Applications with Unacceptable Plans cannot be funded – must revise plans!**

30

Requirements for NIH-Defined Phase III Clinical Trial Applications

- **Progress Reports need to include**

Both:

- **Enrollment Table**
- **Statement in text about progress in data analyses for sex/gender and ethnicity/racial effects.**

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Complying with the NIH Inclusion Policy

- **Principal Investigators**
- **Review Staff and Reviewers**
- **Program Staff**
- **Grants Management Staff**
- **NIH Tracking and Inclusion Committee**
- **Congress**
- **Public**

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Monitoring Compliance with the NIH Inclusion Policy

2001 Biennial Report: Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research

http://www4.od.nih.gov/orwh/salmonrpt.pdf

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Resources and Getting Help

- **PHS 398 Instructions**

http://grants1.nih.gov/grants/funding/phs398/phs398.html

- **PHS 2590 Instructions**

http://grants1.nih.gov/grants/funding/2590/2590.htm

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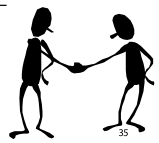
Resources and Getting Help

- Inclusion of Women and Minorities – Implementation Page

http://grants1.nih.gov/grants/funding/women_min/women_min.htm

- CONTACT PROGRAM STAFF!



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NIH Publication No. 03-7036