September 27, 2001

Dear Dr. Garcia,

Very shortly the funding of the Centers for Research to Reduce Oral Health Disparities will occur. To help you in your planning and to assist you in your thinking about the task ahead we've attached the Terms and Conditions of the cooperative agreement for your center. These Terms, developed by NIDCR staff, have been reviewed and approved by the Office of the Director. NIH and they, along with administrative terms and conditions of award, will be part of the notice of grant award that will be forwarded to your business office. In general, these terms and conditions address the implementation of NIH policy pertinent to the conduct of your research, including any clinical trials. They also reiterate specific goals and objectives of this initiative that were stated in the RFA. In addition, they indicate which projects are and are not being supported with funds from the NIDCR. And, finally, they spell out the rights and responsibilities of each of us in our collaborative venture. We ask that you review them very carefully.

We also want to bring to your attention several other points. First, these cooperative agreements are not being funded under expanded authorities. Basically this means that NIDCR staff must approve any significant rebudgeting. Significant rebudgeting occurs when expenditures in a single direct cost budget category deviate (increase or decrease) from the categorical commitment level established for the budget period by more than 25 percent of the total costs awarded. Other requirements include the fact that the ability to carry funds over from one year to the next must be approved by NIDCR staff. There are other conditions and reporting requirements as well, so please consult with staff in your institution’s Office of Sponsored Research to fully understand all of the requirements related to being excluded from Expanded Authorities. What we are aiming at here is to make sure that large deviations in the expenditure of funds are justified and approved.

Second, the initial funding period is for 10 months but the amount granted will be that for 12 months (i.e., the new start date for year -02 will be 8/1/02 but you will receive the same amount for the first year as though the start date was 9/30/02). We are doing this to take some of the pressure off of our Grants Management and Program staffs at the end of the year to review progress reports and make any necessary administrative decisions for continuation funding. These are very complex grants and in doing this we will be able to avoid “bumping” into the end of the fiscal year and potential hurdles with trying to get the awards out. This means that the total grant period will be for 6 years and 10 months. If necessary, we will be able to adjust it by approving a 2 or more month no-cost extension of the grant at the end.
Finally, we ask that you provide our Grants Management staff with any and all materials that they have requested. Awards cannot be made until all information requested by them are received (e.g., IRB approvals, Other Support pages, etc).

We hope this information is helpful to you. Please feel free to contact me if you have any questions. In the meantime, we’re looking forward to getting started, as we are certain that you are.

Best wishes,

Ruth Nowjack-Raymer, M.P.H., Ph. D.
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Division of Population and Health Promotion Sciences
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CC: Dushanka Kleinman
Martin Rubinstein
A. General Conditions

The NIDCR has determined that it will support this project as a cooperative agreement. Within a cooperative agreement, a partnership relationship exists between the awardee and the NIDCR. Each party to this partnership will have rights and responsibilities as well as a defined working relationship. Assistance using a Cooperative Agreement differs from the assistance provided under a traditional research grant. In addition to the normal programmatic and administrative stewardship responsibilities of the NIDCR Program Official as covered in sections A-G of these terms, the NIDCR anticipates substantial scientific/programmatic involvement by a designated Program Official during performance of the project as described in section H. A single Program Official may function in both roles.

These special Terms and Conditions of Award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, PHS regulations at 42 CFR Part 52 and DHHS grant administration regulations at 45 CFR Parts 74 and 92, as applicable, and other DHHHS, PHS, and NIH Grant Administration policy statements. Further, these terms will be in addition to, and not in lieu of, the customary programmatic and financial negotiations that occur in the administration of cooperative agreements.

Future year funding is contingent upon persistent satisfactory performance with respect to the scientific goals of the Center. The NIDCR reserves the right to curtail, withhold, or terminate support for the center overall, or for individual participating projects or allied participant recruitment centers in situations involving: a) inadequate recruitment, follow-up, data reporting, or quality control; b) a major breach of a study protocol; c) a substantive change in the agreed-upon protocol to which the NIDCR does not agree; d) statistical evidence that a major study endpoint has been reached ahead of schedule in a clinical trial or clinical study; or, e) human subject concerns or ethical issues that dictate a premature termination. Prior to taking such actions, NIDCR will consult with and receive recommendations from an advisory group.

The NIDCR Program Official, in collaboration with the trial Principal Investigator and Executive Committee, as applicable, will have access to data generated under the cooperative agreement. Information obtained from the data may be used by NIDCR for the preparation of internal reports on research activities. However, awardees will retain
custody of and have primary rights to the data developed under the cooperative agreement.

As with all NIDCR-supported research, all publications and reports resulting from activities supported by this award must acknowledge support from the National Institute of Dental and Craniofacial Research, NIH, specifically referencing the grant or cooperative agreement number.

B. Governance And Oversight Of The Center

The principal investigator is ultimately responsible for all administrative activities pertaining to the research conducted within the center. In order to insure continuity in theme and scientific merit of the research, the Principal Investigator will appoint an independent scientific advisory committee consisting of consultants with appropriate research experience and accomplishments, but who are not associated with the participating institutions. This committee will conduct an annual review of the: (1) broad goals and accomplishments of the center including outreach, mentoring, career development and training activities; (2) assess interim progress of all scientific projects and their relevance to the broad objectives of this initiative; and (3) aid in the review of pilot projects proposed after initiation of the grant. The advisory committee may, as appropriate, serve as an informal review group for grant applications or contract proposals resulting from research conducted within the center and, if funded, planned for administration under the umbrella of the center. The Program Official or designee will serve as an *ex officio* member of the steering committee. This committee may not serve in lieu of a Data and Safety Monitoring Board (DSMB), however members of the DSMB may serve on the steering committee.

C. CRROHD As A National Resource

Receipt of a CRROHD carries with it the expectation that the center will provide the impetus and core for research and training networks on health disparities. These networks can take on many forms and serve a variety of specific research areas. The purpose of the networks is to leverage the resources available through the center, and in so doing to, facilitate research and research training by linking these resources with other sites around the country where the necessary expertise, facilities, capabilities and research opportunities may not be readily available. Another function of the networks is to enhance the opportunities by center staff for access to populations and communities that may not be available locally.

Research and training networks may be fostered by increased collaborations across the health professions (e.g., dentistry, medicine, dental hygiene, nursing, pharmacy, nutrition, behavioral and social sciences, public health) both within and between institutions as well as between the health professions and social services (e.g., State and Local health and health financing agencies) directed at health promotion. Funds provided through the cooperative agreement are restricted to the support of research activities. Nevertheless, it
is expected that each center will include specific plans for developing training and career enhancing opportunities through partnerships with one or more minority institutions (e.g., Historically Black Colleges and Universities, Hispanic serving institutions, Tribal Colleges and Universities) as well as with dental schools that serve primarily as institutions to train dentists and dental hygienists. The Principal Investigator, in consultation with the Program Official, will develop a plan to use the center as the hub of a network of institutions, linking with both minority institutions as well as non-research intensive dental schools. Included in the plan will be specific ways that existing training grants will be used to increase the diversity of the research workforce for the center. In instances where such training support does not exist, the Principal Investigator will develop a plan that includes the attainment of funding for training.

Another aspect of the center as a national resource for research on reducing oral health disparities is the expectation that the Principal Investigator will identify new opportunities for research and seek funding for the research from federal and state agencies as well as from foundations and other private sources. The center will also serve as a resource for research on reducing oral health disparities funded through other research teams at other institutions by making available both intellectual and physical capabilities (e.g., special populations, databases, experimental design and analysis capabilities, biological assays, etc.) in carrying out the specific aims of funded research. Again, in consultation with the Program Official, the Principal Investigator will develop an action plan to advertise the center’s capabilities and to reach out to developing and existing projects.

D. Annual Meetings

An annual meeting of CRROHD directors and key staff will be held in Bethesda. The purposes of the meeting are to: (a) share scientific findings and identify and discuss emerging research opportunities; (b) develop collaborative research activities amongst the centers; (c) discuss and resolve administrative issues among the center directors as well as other participants invited by the Institute; (d) obtain input on the on-going formative evaluation of the centers; and (e) provide training experiences for developing members of the center’s research team. Each Principal Investigator is expected to participate in the development of the agenda and to serve as the representative of his/her center. Except in rare instances, the meeting is open to all individuals.

F. Evaluation Plan

Congruent with the objectives of “Healthy People 2010” the purpose of the research supported under this cooperative agreement is to support research that will ultimately reduce health disparities. Thus it is important that an evaluation process be in place that will allow an assessment of progress toward reducing health disparities through the research conducted by the centers. In this regard, the Principal Investigator or his/her designee will cooperate with NIDCR staff in designing and implementing an evaluation that not only assess progress of individual center activities toward the goal of reducing health disparities but which also provides an overall assessment of the entire center
G. Special Terms Specific for Each Center

The NIDCR is providing funds to support the following projects and cores included within the application for the center:

Project 1 – (Pl: Avrom Spiro) – Oral health related quality of life in children and adolescents
Project 2 – (Pl: Nancy Kressin) – Decreasing rates of early childhood caries through health care
Project 3 – (Pl: George Acs) – The effect of severe early childhood caries (S-ECC) and comprehensive dental intervention on weight of children
Project 4 – (Pl: Anne Tanner) – Microbiota of children with oral health disparities

Administrative Core
Biometry Core
Clinical Core
Training Core

Funds in the amount of $299,682 (DC & IDC) for Projects 2 and 3 are restricted from use until the concerns raised during peer review are addressed. The principal investigator is encouraged to use pilot funds to address these concerns. Once additional information is collected, a new application, regarding these projects, including a countersigned face page, budget pages, and budget justification pages should be submitted for each project. The application should contain details of specific steps taken to address reviewers concerns along with any changes in the experimental design of the project, including changes in protocol, and a budget justification. While the level of budget to support these projects may change with changes in experimental design and/or protocol, the overall budget for the center may not exceed the approved awarded amount. This information should be reviewed and approved by the External Advisory Committee for the center and then forwarded to the Program Official for review, comment and possible approval. If the External Advisory Committee does not consist of individuals with appropriate scientific expertise, ad hoc members should be added for these reviews. In either case, the Principal Investigator is encouraged to contact the Program Official for approval before conducting the review.

H. Additional Cooperative Agreement Terms and Conditions

1. Awardee’s Rights and Responsibilities

Awardees will have the usual responsibilities of award recipients including: a) defining research objectives and approaches; b) protocol development; development of data collection instruments; c) participant recruitment and follow-up; d) data collection and quality control; e) incorporation of ancillary studies; f) interim data and safety monitoring; g) data analysis and interpretation; and, h) preparation of study presentations and publications. Awardees will have responsibility for developing recruitment milestones expected to be met at specific time periods as well as accrual goals for
women, minorities and children (as appropriate). The design, methods, and procedures of any clinical trials will be detailed in an awardee-prepared and maintained, study-adopted Manual(s) of Operations. Awardees will have responsibility for following the protocol, collaborating with other awardees, as appropriate, and collaborating with the NIDCR Program Official.

The Principal Investigator will have primary responsibility for directing the overall research efforts of the trial. S/he is responsible for the overall conduct of the clinical trial and for providing scientific, technical, and administrative leadership to the study. S/he will have lead responsibility for planning and directing all phases of the study and for using the study's resources. In carrying out these responsibilities, the Principal Investigator will actively seek advice from all of the study's components, including the NIDCR Program Official.

The Principal Investigator is reminded that adequate protection for human subjects in research is an essential requirement for research supported by the National Institutes of Health. Grantee institutions, and each subordinate entity to the grant, whether institutions or independent investigators, should agree that the rights and well being of human subjects involved in research under this cooperative agreement shall be protected in accordance with 45 CFR 46. As a condition of award, grantees and affiliated performance sites are required to designate an Institutional Review Board (IRB) and possess an applicable assurance of compliance that has been approved by the Office for Human Research Protections (OHRP) of the NIH.

In addition, awardees have primary responsibility for ongoing safety monitoring commensurate with participant risks. In this regard, awardees must implement a structured adverse event determination, monitoring, and reporting system, including standardized forms and protocols for referring and/or treating participants experiencing adverse events. Furthermore, it is the awardee's responsibility to report adverse events to the NIDCR and participating IRB's, as well as to a Data Safety and Monitoring Board (DSMB) and the Food and Drug Administration, as applicable, in a timely manner. It is the awardee's responsibility to develop trial stopping guidelines and, where applicable, modify them in accordance with DSMB recommendations.

If a DSMB is needed to adequately ensure participant safety or is mandated by NIH and NIDCR guidelines, it will report directly to the Institute. Awardee's responsibilities relative to DSMBs include the following:

- providing all logistical and budget (via the grant) support necessary for board operations including meetings, conference calls, mailings, and minutes;
- keeping NIDCR appraised of all DSMB activities and recommendations and providing NIDCR with a copy of meeting minutes;
- furnishing the DSMB with draft trial stopping guidelines;
- notifying the DSMB of all trial participant "adverse experiences" as they become aware of them;
• furnishing the DSMB with relevant data and all requested materials in a timely manner; and,
• responding to DSMB recommendations endorsed by the NIDCR.

Additional guidelines detailing the establishment and operation of DSMBS for NIDCR-sponsored clinical trials can be found at:
http://www.nidr.nih.gov/research/CTP/dsmb.htm

2. NIDCR Rights and Responsibilities

The NIDCR will provide substantial scientific/programmatic to the Principal Investigator through a Program Official designated from the Division of Population and Health Promotion Sciences, NIDCR as well as through expertise from the Planning, Evaluation and Legislation Branch, OSPA, NIDCR. The Program Official’s name will appear on the notice of grant award. The Program Official will have overall responsibility to assure the scientific and technical integrity of the project on behalf of the Institute. It is emphasized that the role of the NIDCR Program Official will be to act as a facilitator and not to direct the activities of the study investigators. The representative from the Planning, Evaluation and Legislation Branch will provide guidance with respect to the evaluation of the center’s activities as well as serve as the contact point for information used in evaluating the entire program. In both instances, the NIDCR staff will participate with and assist, but not direct the activities of the center. The Program Official will assist:

• the Principal Investigator in the nomination and selection of an independent Data and Safety Monitoring Board, if applicable;
• the Principal Investigator in assuring that participant information booklets, press releases, and other publicity activities are properly prepared and disseminated;
• the Principal Investigator in the identification of additional participating research centers to form the research and training networks required by the RFA;
• the Principal Investigator or Study Chairperson and Executive Committee, as applicable, in technical aspects of clinical trial protocol design and implementation as well as in the design of other research activities;
• the Principal Investigator and Steering Committee in routine performance monitoring of the entire study including matters of quality control within and among various components, and in the determination of inadequate patient recruitment or failure to comply with the protocol on the part of participating centers;
• the Principal Investigator or Publications Committee, as applicable, in the preparation and review of study results for publication;
• the Principal Investigator and Executive Committee, as applicable, in oversight of all participant safety monitoring activities;

• the Principal Investigator in the design and implementation of evaluation studies; and

• the Data and Safety Monitoring Board, where applicable, as an ex officio member

3. Collaborative Responsibilities

It is anticipated that the Principal Investigator will provide leadership and direction in day-to-day affairs working with an Executive Committee or similar body. It is anticipated that decisions aimed towards achieving research objectives of the project will be made by the Executive Committee under the leadership of the Principal Investigator. Voting membership for the Executive Committee will include the NIDCR Program Official. Once established, the Executive Committee will provide general oversight and direction for the center as well as routine performance monitoring. The Executive Committee will develop general policies concerning: a) evaluation of overall center and center-specific performance; b) subcommittee or working group structure and membership; c) publications; d) access to data; e) agendas for group meetings; and f) schedule and content of Executive Committee meetings. The Executive Committee will also be charged with establishing center goals and other measures of center performance including data quality and timeliness of data entry where applicable.

4. Special Terms for Centers Involving Clinical Trials

These terms are consistent with those for all NIDCR-supported clinical trials.

a. Trial Organization and Management

Some Centers may include one or more clinical trials aimed at assessing interventions aimed at reducing oral health disparities. These may be either single- or multi-center trials. For single center clinical trials funded through cooperative agreements, it is anticipated that decisions aimed at achieving the research objectives of the trial will be made by the Principal Investigator in consultation with the NIDCR Program Official. The Principal Investigator, in concert with the NIDCR Program Official, will be responsible for establishing recruitment milestones expected to be met at specific time periods, accrual goals for women, minorities and children (as appropriate), retention goals, and other measures of performance including follow-up activity, data quality and timeliness of data entry.

For multi-center clinical trials funded through cooperative agreements, it is anticipated that the Study Chairperson will provide leadership working with an Executive Committee. Voting membership for the Executive Committee will include the Study
Chairperson, the NIDCR Program Official, Director of the Coordinating Center and other Resource Core Centers, as applicable, and a small group of representatives from participating enrollment centers, including the Principal Investigator of the CRROHD if the Executive Committee is operated outside of the umbrella of the CRROHD. The Executive Committee as appropriate will establish other committees, such as the Publication Committee, as well as working groups. Once established, the Executive Committee will provide general oversight and direction for the trial as well as routine performance monitoring. The Executive Committee will develop general trial policies concerning: a) evaluation of overall trial and center-specific performance; b) subcommittee or working group structure and membership; c) publications; d) access to data; e) agendas for group meetings; and f) schedule and content of Executive Committee meetings. The Executive Committee will also be charged with the establishment of recruitment milestones expected to be met by centers at specific time periods, accrual goals for women, minorities and children (as appropriate), retention goals, and other measures of performance including follow-up activity, data quality and timeliness of data entry. Actions of the Executive Committee, if operated outside of the umbrella of the Center, will be reported to the CRROHD’s Principal Investigator in a timely manner.

b. Accrual Goals and Recruitment Milestones

Prior to making an award, specific and mutually agreed-upon accrual goals for women, minorities and children (as appropriate) as well as recruitment milestones expected to be met by enrollment center(s) at specific time periods will be part of the Terms and Conditions of Award.

c. Reporting Requirements and Performance Reports

In addition to the annual and final reports required of any grant, all NIDCR-supported clinical trials, including those funded through cooperative agreements, must provide initial and ongoing trial information in support of NIH’s Clinical Studies Database and other reporting requirements. The intent of the Clinical Studies Database maintained by the National Library of Medicine is to provide health practitioners and the lay public readily accessible information on NIH-supported clinical research studies. Data elements to be provided by investigators prior to an award being made and quarterly thereafter include initial and relevant follow-up information on the following:

- A shortened study title in easily-understood language
- A brief summary of the study written for the public
- Study phase (i.e. Phase I, II, III or IV)
- Study type using one or more of the following designations: Genetic, Diagnostic, Preventive, or Treatment
- Study design using one or more of the following designations: Community Intervention Trial,
- Concentration-Response Design, Cross-Over Study, Dose Discontinuation Study, Dose-Response Design,
- Double-Blind Study, Factorial Design, Multicenter Study, Open Label, Parallel Designs, Placebo-Controlled Trial,
- Random Allocation, Randomized Control Study, Sequential Analysis, or Single-Blind Method
- Name of the disease or condition under study
- Categorization of the intervention type (i.e. drug, device, vaccine, procedure, behavior, biologic)
- Name of the drugs, devices, procedures, biologics, or vaccines tested in the study
- Inclusion criteria including minimum and maximum age, gender, and minority status
- Study contact information including name, title, phone number, and address
- Name and location of study centers
- Expected or actual study completion date
- Designation of recruitment status (i.e. not yet recruiting, recruiting, no longer recruiting, or completed)
- Accrual activity at each study location
- Overall study accrual of women, minorities, and children as applicable

For clinical trials that propose to recruit 100 or more subjects (in one institution or in a multi-center project), the progress reported in the annual application(s) for non-competitive renewal must include center-specific and overall updates of progress toward:

a) recruitment milestones and accrual and retention goals; b) other measures of performance including follow-up activity, data quality and timeliness of data entry; c) proportion of laboratory and/or repository specimens collected and shipped to resource centers (as applicable); d) proportion of laboratory and/or resource center tests or readings completed and data entered (as applicable); and, e) scientific contributions toward trial goals. These reports will be used by the NIDCR to determine funding requirements for remaining budget periods and to develop future budget awards.

d. Data and Safety Monitoring Boards

An independent Data and Safety Monitoring Board (DSMB), to be appointed by NIDCR, will review progress at least annually and report to NIDCR. A Principal Investigator may not begin enrollment of participants until after the DSMB has reviewed the study protocol, including data capture and analysis plans, and recommended to the NIDCR that the research proceed. Members of the DSMB review the study protocol as well as data and safety monitoring plans. In addition, they monitor data as they accumulate, and make recommendations to the Institute and Principal Investigator regarding appropriate protocol and operational changes. These groups are advisory to the NIDCR and they do not play the role of initial review groups for the purpose of scientific merit evaluation nor do they replace the need for Institutional Review Boards (IRB). DSMBs play an essential role in protecting the safety of trial participants and assuring quality research immediately prior to and during the conduct of the clinical trial. In order to provide this assurance, all clinical trials involving randomization to alternative treatments must have a mechanism in place for reviewing the approved protocol, subject protection procedures including informed consent, recruitment and retention procedures, enrollment progress,
data capture and analysis plans, and interim data in the context of the most recent scientific literature. DSMBs are critical elements in the decision-making process. The DSMB will examine data for any untoward effects of the intervention under assessment on participants. The DSMB will have the responsibility of reporting to the NIDCR the occurrence of untoward effects, any human subject ethical issues, or if statistical significance is reached in one of the major study endpoints before the planned end of the trial. Details of the organization, roles and responsibilities of the DSMB are available through the NIDCR web site at http://www.nidcr.nih.gov/research/CTP/clinical_trials.htm or from the Program Official.

I. Arbitration for Resolution of Differences

Disagreements that arise between award recipients and the NIDCR in scientific or programmatic matters falling within the scope of the award and which significantly restrict trial progress, may be brought to arbitration. An arbitration panel will be composed of three members, one selected by the Principal Investigator or Study Chairperson, as applicable, a second member selected by the NIDCR, and a third member with expertise in the relevant area selected by the two prior members. Panel members shall not be affiliated with the trial. The panel will decide on the issues as presented and provide their judgment in writing to both parties. While the decisions of the arbitration panel are binding, this special arbitration procedure in no way affects the awardee's right to appeal an adverse action in accordance with the PHS regulations at 42 CFR part 50, Subpart D and HHS regulation at 45 CFR part 16.