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HARVARD SCHOOL OF DENTAL MEDICINE

DEPARTMENT OF ORAL HEALTH POLICY AND EPIDEMIOLOGY

29 January 1997

Rec'd CEMBS
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Program Administrator
Chemical Exposures and Molecular Biology
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
PO Box 12233
Research Triangle Park, NC 27709

Approved for
no-cost extension
Gwen Coll

RE: Grant 5RO1 ES06000-04

Dear Dr. Collman,

Our current funding expires on March 31, 1997 and we are hereby requesting a continued no-cost extension. Presently, we have collected 164 prevalent (with complete fluoride histories) and 80 incident cases which falls short of the sample size needed to rule out a relationship between fluoridation and osteosarcoma.

As you know the bulk of the new cases are being gathered by the National Cancer Institute, 80 such cases, "incident" cases, have been recruited to date and 50 are projected for 1997, plus 50 for 1998. At a 75% completion rate (since 25% of cases do not have complete fluoride history) we would then anticipate 150 incident cases, which when added to the 164 prevalent cases would result in 314 total cases in our final data set by Dec 1998. Our power calculations show that we need 415 cases to achieve an upper bound of the confidence interval of 1.5. Moreover, in order to state no association between fluoride and osteosarcoma with an upper bound of the confidence interval below 1.3 we will need over 711 cases depending on the exposure definitions. **Because of the importance of the question at hand, we think the policy implications of reporting that the relative risk maybe higher than 1.5 would have consequences for fluoridation health policies.** To make a statement that there is no association, we need to show that there is no association for various scenarios of exposure definitions and varying exposure prevalence.

Accordingly, it is our estimation that we need to gather approximately 100 additional cases with a 75% complete fluoride history. These would be prevalent cases for which we will use the same methodology that we have used to obtain the 164 prevalent cases to date.

With the requested extension we believe we can obtain 38 of the needed cases and complete all the analysis for three published papers that report significant progress on the project. With this productivity we then believe that we will need some additional funding to obtain the final remainder of the cases.

The following is a hospital by hospital delineation of the progress we have made:

Chicago Rush: To date, paperwork has been received on 14 cases, 8 tumor controls, 5 orthopedic controls, one case refusal, and one tumor control refusal. More subjects have been identified and will be completed after their surgery or during follow-up care.

University of Chicago: Completed questionnaires have been received for 17 cases, 11 tumor controls, and two orthopedic controls. Several cases and tumor controls have been identified and they will be interviewed at the time of surgery or follow-up during the coming months.

Washington, DC, Children's Hospital/Washington Hospital Center: To date, this site has completed 2 questionnaires for tumor controls. Several more cases and tumor controls are pending surgery at Washington Hospital Center and Children's during the coming months. At Washington Hospital Center, training of site staff, including the site coordinator for Children's Hospital, and an interviewer from Westat occurred over the course of several weeks. The training included introduction of the study and the team members.

Cleveland Clinic: Currently this site has completed a total of 3 cases. Several cases and tumor controls have been identified and are pending completion during the coming months. A new nurse has been hired and trained and prepared for certification. Resumption of subject enrollment has been delayed by the need for the site's IRB to reapprove the study and the revisions to the consent process that had been requested. It is expected that this site will resume enrolling and interviewing subjects during December.

Creighton University: Completed paperwork has been received for a total of 2 cases and 4 tumor controls. During November one new osteosarcoma case was reported, but the questionnaire has not yet been delivered.

UCLA: To date, paperwork has been received for 16 cases, 7 tumor controls, and 10 orthopedic controls. The fellow who served as site coordinator completed his fellowship at UCLA and left at the end of July. Subsequently in early August, Dr. Eckardt indicated that he was unable to continue with the study. A lack of available staff and *[personal privacy issue]* were the reasons given for discontinuing the study. It is hoped that arrangements can be made to continue the study at UCLA if Dr. Eckardt is willing and if sufficient hospital staff can be made available. Efforts are being made to continue the search for matching autopsy controls.

University of Florida: Data has been received for 17 cases, 14 tumor controls and 10 orthopedic controls, and the paperwork for one autopsy control. The site also reports having several more cases and tumor controls who have been enrolled or identified and who will complete the questionnaire in the coming months.

Massachusetts General Hospital, Boston: Data has been provided for 6 cases and 1 tumor control. Several more patients have been identified and have given consent to participate. The coordinator has reported several controls who are pending completion. The specimen coordinator has also discussed the possibility of utilizing iliac crest specimens obtained from bone donors in place of the similar specimen from autopsy subjects.

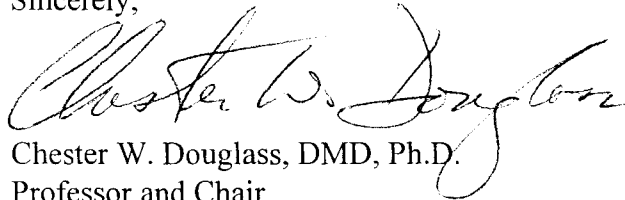
On October 17, 1996, a conference call was held with the NCI Project Officer, the study pathologist, Westat personnel, and Harvard faculty, Drs. Douglass, McGuire and Joshipura. The purpose was to further discuss possible sample size revisions, power calculations, and their expected impact on the study schedule and budget. It was decided to increase the sample size and to explore possibilities for expanding the number of study sites to increase subject enrollment.

Westat staff has sent a memorandum to the collaborating surgeons asking for suggestions concerning incentives for completing matched case sets, suggestions for improving the rate of recruitment for the study and for recommendations of additional sites that could potentially be added to the study. Follow-up calls will be conducted with the collaborating surgeons to obtain their opinions concerning suggestions for additional sites and increased incentives to site coordinators. Also discussed with each collaborating surgeon and Dr. Clarke Anderson (the study pathologist) will be the option of substituting donor bone iliac crest specimens in place of autopsy specimens.


Dr. Da Silva's minority supplement on this project is also delayed. The portion of the project that he is working on is dependent on the collection of the prospective data. As was previously explained there is a lag in the data collection and therefore Dr. Da Silva's project cannot move forward until the data set has been acquired. Dr. Da Silva is continuing to work on the collection of water samples and the measurement of fluoride levels in the samples collected.

Thank you for your attention to this request. If you have any questions please do not hesitate to call me.

Sincerely,



Chester W. Douglass, DMD, Ph.D.
Professor and Chair



Susanne Churchill, Ph.D.
Director, Sponsored Program Administration
Harvard Medical School

cc: Mary Cassesso
Associate Dean of Administration
Finance
Harvard School of Dental Medicine