Supporting Statement A For:

Follow-up of Kidney Cancer Patients from the Central European Multicenter Case-Control Study (CEERCC) (NCI)

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A. JUSTIFICATION

A.1 Circumstances Making the Collection of Information Necessary

The Occupational and Environmental Epidemiology Branch of the Division of Cancer Epidemiology and Prevention, of the National Cancer Institute (NCI) developed the idea for the Central and Eastern European Multicenter Case Control study, which was completed in 2002 in accordance with the mission to develop scientific information and concepts and disseminate the acquired knowledge regarding risk factors for kidney cancer. To this end, the Occupational and Environmental Epidemiology Branch conducts studies of disease etiology, acquires knowledge and conducts research, and encourages publication of scientific findings from these studies. Section 412 of the Public Health Service Act (42 USC *§* 285a-1) and section 413 (42 USC 285 a-2) that authorizes the collection of the information.

Survival from kidney cancer is highly dependent upon stage at diagnosis. The average 5-year survival rate for 1996-2002 from 17 SEER geographic areas is 60-65%. When the cancer is confined to the primary site, 5-year survival is very high (90.4%). However, if regional and distant metastases are observed, 5-year survival is much lower, 61% and 9.5% respectively. Renal cell carcinoma is among the most resistant tumors to therapy. The Central and Eastern European multicenter case-control study offers the opportunity to identify determinants that predict 5-year survival among kidney cancer patients. Since survival has not improved substantially over the last decades, any improvements upon current methodologies to identify prognostic indicators could have the potential to improve survival rates among kidney cancer patients.

This request is to conduct a follow-up study of kidney cancer patients in the high risk region of Central and Eastern Europe. This study would be conducted through the follow-up of a group of patients with kidney cancer who were previously enrolled in an NCI funded study

entitled, “Occupational, Genetic Susceptibility, Kidney Cancer: Central European Case-Control Study” (01-C-N063). The Central and Eastern European Renal Cancer Study has been out of the field for four years and data analyses of the main study are complete. Ongoing analyses of genetic susceptibility markers, gene-environment interactions, and tumor heterogeneity markers are in the final stages. To date, 12 papers have been published or have been submitted for publication (Attachment 1), at least 15 more are in preparation.

Like the case-control study, this follow-up study would be conducted in six countries, including Romania, Poland, Russia, and the Czech Republic. In each study center, cancer-related information will be extracted from vital statistics, cancer registry and/or medical records and be linked with the previous patient series. If patients or if their next-of-kin agrees under the circumstance that the patients are deceased, they or the next-of kin will be interviewed with a brief questionnaire. The overall aim is to investigate the role of established and potential determinants of survival by abstracting information from vital statistics, cancer registries, and medical records and by interviewing participating cancer cases or their next of kin when possible about risk factors that occurred after cancer diagnosis. We also plan to investigate the role of genetic factors that we hypothesize may affect prognosis and survival among these patients.

First we will conduct a pilot study to determine the feasibility of collecting survival information including 5-year survival status, date of death, cause of death, and date of last follow-up (if alive) on 220 cases from the six collaborating centers. This pilot study of 220 cases is considered clinically exempt by NIH (CE08-05-01) and was approved on 05/07/2008. Information on 50 cases will be obtained from Olomouc and Moscow, and 30 cases from the remaining centers (Bucharest, Prague, Brno, and Lodz) using a list of cases provided by the NCI to each study center. The feasibility of abstracting information including surgical and medical treatment procedures used to treat primary disease, recurrence and progression of primary

disease will also be determined. Abstracted information collected and translated into English in addition to a report describing any obstacles to obtaining information requested will be provided by the International Agency for Research on Cancer (IARC) to the NCI. If investigators in each study center are able to obtain the information requested from 80% of the cases in the feasibility study, we will proceed with the full survival study of all remaining cases (N=1100-220=880; 440 cases per year). The objectives of the main study are: (1) to assess the 5-year survival status of kidney cancer patients in the CEERCC study; (2) to assess prevalence of recurrent disease and progression; (3) to investigate additional patient- tumor- and genetic determinants of 5-year survival in cases. A new questionnaire will be administered to all subjects or the next of kin to capture change in smoking habits after the initial diagnosis. Other information will be collected from data available from the vital statistics office, cancer registry, and will be abstracted from clinical records.

To be eligible for this study, patients needed to have been an eligible participant in our previous renal cell case-control study and have been diagnosed with a histologically confirmed renal cell cancer. Participation in this follow-up study is completely voluntary, they may withdraw at any time without affecting the treatment they receive. No penalties will result if the subjects decide not to respond either to the information collection as a whole, or to any particular questions.

A.2 Purpose and Use of the Information Collection

In addition to publications of benefit to the scientific community, data collected will be used to assess the 5-year survival status of kidney cancer patients in the CEERCC study, assess the prevalence of recurrent disease and progression, and to investigate patient, tumor and genetic determinants of survival in cases. This information will be used to identify prognostic indicators

of survival that will be used for evaluating high-risk patients and reduce disease mortality. The information will be used by researchers at the NCI and at IARC. The information concerning participation of a subject in this study will be kept confidential and used only for scientific purposes in accordance with applicable law of (Czech Republic, Poland, Romania, or Russia) and the United States state and federal law. Since the CEERCC study is the largest study of kidney cancer completed to date with biological samples collected, there is no other source from which to obtain such data.

Information that will be collected will include patient related factors (age, sex, tobacco usage), tumor related factors (anatomic site, histology, disease staging, tumor size, extension) and treatment related factors (surgery, radiotherapy, chemotherapy, resection margins). Biologic prognostic characteristics of kidney cancer subsets will be measured and correlated with mortality to identify predictive indicators of disease outcome. The four outcomes we intend to evaluate specifically include; 1) Renal Cell Carcinoma (RCC) death, 2) Alive at 5-years with disease recurrence (same clinical stage or disease independent of primary tumor), 3) Alive at 5-years with disease progression (disease presents at higher clinical stage than primary diagnosis), and 4) Censored (alive at 5-years, lost to follow-up, or died of other causes).

Before conducting the main study, a pilot study will be conducted to evaluate the success rate to obtain data from various sources and to identify the optimal method of linkage in each center, evaluate the forms developed for data abstraction and compare their application to data abstraction from different sources, investigate the feasibility and success rates for contacting patients and/or the patient's family and of conducting interviews with them, to assess accuracy of interview data by comparing it with information obtained passively from medical records or cancer registries, to evaluate and compare methods used for clinical follow-up evaluation across centers, and lastly to estimate costs for each center for the complete follow-up component.

As in the case-control study, physicians and experienced medical staff will be employed to abstract hospital records, pathology reports, and treatment information. After we distinguish the types of follow-up protocols used and procedures followed in each country, we will develop a definition of those cases confirmed to be disease-free (using high-confidence methods, i.e. CT, PET, laboratory methods other), and patients for whom follow-up was not confirmed, incomplete, or undetermined ("low confidence confirmation") so that we can stratify by this variable and conduct restricted analyses. We plan to collect information on methods used to evaluate disease status. Treatment variables will be grouped into broad categories and will be used as adjustment variables. Lastly, we will initiate follow-up at date of diagnosis and collect survival at 5-years, controlling for treatment and perhaps with time dependent co-variables for treatment duration as needed. We will not discount any time during cancer treatment towards survival as this could make more advanced cases with longer treatment duration incorrectly appear to have a longer disease-free survival.

A.3 Use of Improved Information Technology and Burden Reduction

An interviewer will administer the questionnaire (pen and paper questionnaire) while the patient is in the hospital or at home. The questionnaire will contain the patients name or any identifying information and it will be coded with the personal identification code from this point onward. Pen and paper questionnaires will be used because electricity may not always be available in all areas and availability can be inconsistent. In cases where telephone administration might be used, the questionnaire will be read to the participants verbatim since the script is included as part of the questionnaire. Other data collection instruments, such as abstraction forms, are completed by trained medical personnel as in the etiologic case-control study conducted previously. These additional forms will never contain the patients name or any

personal identification information. All forms will be coded with the personal identification code. Privacy of all information collected from cases will be strictly used for the purposes of the study. The information concerning participation of a subject in this study will be kept confidential and used for scientific purposes All questionnaires and abstracts will be coded prior to the interview and data collection so that information will not be linked with personal identifiers. Data entry will take place at IARC and data will be merged with the MS Access database. Data will be stored electronically at IARC and then transferred without identifiers to Information Management Systems in Rockville (IMS). We will pursue a Privacy Impact Assessment to assess and resolve the privacy and security risks of the electronic system.

A.4 Efforts to Identify Duplication and Use of Similar Information

The Central and Eastern European Case-Control Study was completed in 2003. The purpose of this study was to investigate the role of lifestyle factors, medical conditions, occupational exposure history, and diet in relation to their effects on the outcome of kidney cancer patients in Europe. Blood was collected as a source of genomic DNA which has been used to identify markers of genetic susceptibility, and tumor tissue has been collected to identify biomarkers of disease etiology. This wealth of information we have generated initially to investigate in reference to disease etiology, can now be used identify determinants of survival. The only additional information required to complete this type of analysis will include vital statistics information and potential modifiers of survival including histopathologic characteristics of the tumor and treatment information. This is the only study in the world that has collected such a large quantity of information on lifestyle factors, occupational exposures, genetic susceptibility and RCC tumor markers that could enable identification of new determinants of kidney cancer

recurrence, progression, and survival. Therefore in summary, there is no replication of study type or the information we propose to collect.

A.5 Impact on Small Businesses or Other Small Entities

This information collection does not involve small businesses or other small entities.

A.6 Consequences of Collecting the Information Less Frequently

Information for this research study will only be collected once. We already have collected a wealth of information on risk factors for kidney cancer including lifestyle factors inherited genetic susceptibility markers, and somatic mutations in tumor tissue. The consequences of not conducting this study are that we could not use this information to identify determinants of survival because we would not know their outcome and how these biomarkers may predict survival, disease progression, and response to cancer treatments.

A.7 Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The proposal is consistent with the information collection guidelines in 5 CFR 1320.5.

A.8 Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A 60-day Federal Register notice soliciting comments on the Follow-up of Kidney Cancer Patients from the Central European Multicenter Case-Control Study prior to initial submission to OMB was published in the Federal Register on November 3, 2008 (Volume 73, No. 213, p. 65387) and allowed 60-days for public comment. There was one public comment received from B. Sachau (losinghome@aol.com) which questioned why US tax dollars are being spent on a study located in Europe. The investigator responded directly to the comment on 12/19/08 stating that this study costs less money to conduct in central Europe than in the US

since previous data has already been collected. The investigator added that since this region has the highest rates of kidney cancer in the world a study in this area would provide a wealth of data in terms of the causes of kidney cancer.

During the pilot study planning phase, we worked primarily with our collaborators from the Central European Case-Control study from NCI and IARC. However, we also obtained additional statistical advice from the following individuals.

Dr. Ruth Pfeiffer PhD -Senior Investigator –
Statistical advice, study design and power calculations, and data analysis.
Biostatistics Branch, DCEG, NCI, NIH
(301)594-7832; pfeiffer@mail.nih.gov

Richard Hayes PhD. DDS - Senior Investigator –
Study design, methods for collection of survival and treatment data, and advice in how to judge quality of data collection from the pilot study.
Occupational Epidemiology Branch, DCEG, NCI, NIH
(301)435-3973; hayesr@mail.nih.gov

Dr. Ola Landgren MD, PhD – Investigator –
Survivial studies that are hospital-based, collection of survival and treatment data, protocol review, and data analysis methods.
Genetic Epidemiology Branch, DCEG, NCI, NIH
(301)496-5786; landgreno@mail.nih.gov

A.9 Explanation of Any Payment or Gift to Respondents

This information collection does not involve payment or gifts to respondents.

A.10 Assurance of Confidentiality Provided to Respondents

The protocol that was submitted for IRB approval of the pilot study and the survival study (Attachment 2) received IRB approval on 4/17/2008 (Attachment 3). The Privacy Act does not apply to this data collection because the patients are not U.S. Citizens or resident aliens (Attachment 4).

Personally identifiable information (PII) was collected in the original main case-control study in the form of the patient's name, birth date, sex, residency, medical history, tobacco and alcohol use, and treatment. For the "Follow-up of Kidney Cancer Patients from the Central European Multicenter Case-Control Study," these same questions will be asked (Attachment 6). The participants' names will be maintained by the principal investigator at each center but only information by personal identification code will be released to the International Agency for Research on Cancer (IARC) in Lyon France or the National Cancer Institute in the US. The information concerning participation of a subject in this study will be kept confidential and used only for scientific purposes, in accordance with applicable law of (Czech Republic, Poland, Romania, or Russia) and the United States state and federal law. No one except members of our research team will have access to questionnaire data and medical records. Questionnaires will never be labeled with a patient's name, only the study identification code. Any information linking identifiers to an individual's name will be kept locked at all times at each study center. Subject names or personal identifiers will not be used in any reports or released in any way.

The personal identification codes will be created by IARC and they will be assigned to patients by the study center principal investigators. The abstraction form will be coded by the study center principal investigators and will not contain any personally identifiable information, only relevant medical history related to their diagnosis, treatment and outcome from kidney cancer (Attachment 7). No personally identifiable information was collected or will be made available to the IARC or the NCI in this study.

In addition, each participant recruited into the study signs an informed consent which states the voluntary nature of participation and that information they provide will be kept confidential by the principal investigator at each study center. There are two different consent forms, one for the patients with RCC and the other for the next-of- kin (Attachment 5). The

consent form also informs patients that during the interview, they may refuse to answer any questions that make them feel discomfort. Moreover, patients are informed on the new consent document (designed specifically for the follow-up study) that we will ask their permission to collect relevant information from their hospital and cancer registry records. Patients are told that no penalties will result if they decide not to respond, either to the information collection as a whole, or to any particular questions. They are also informed about the study purpose, the procedures involved in the study, and the types of questions that will be asked in this follow-up study. They will also be notified about their potential risks, benefits, assured of confidentiality, and of their rights as participants.

A.11 Justification for Sensitive Questions

The questions asked during the questionnaire are very similar to those answered during the main case-control study. PII will be asked in the form of the patient's name, birth date, sex, residency, medical history, tobacco and alcohol use, and treatment (Attachment 6). No questions about the participant's SSN, salary, reproductive decisions, sexual behavior, religious beliefs, alcohol or drug abuse, or psychological problems will be asked.

We need to collect the participant's name and medical history so that we can link the cases information back to the data obtained during the original case-control study. We also ask some questions about smoking habits at both times to assess the accuracy of their information so that we can compare the accuracy of information obtained from the case at two different time periods, to that obtained from the cases and the next of kin. Lastly, we need to obtain medical history and limited lifestyle habit information so that we can identify determinants of survival to RCC while controlling for histopathologic features of the tumor as potential confounders.

A.12 Estimates of Annualized Burden Hours and Cost

Table A.12 - 1 Estimates of Annual Burden Hours

Type of Respondents	Number of Respondents	Frequency of Response	Average Time per Response (Minutes/Hour)	Annual Burden Hours
Patients	200	1	40/60	133.33
Families (NOK)	240	1	40/60	160.00
Physicians	10	1	15/60	2.50
Totals	450			295.83

Table A.12 - 2 Annualized Costs to Respondents

Type of Respondents	Annual Burden Hours	Hourly Wage Rate	Annual Respondent Cost
Patients	133.33	$17.00	$2,266.67
Families (NOK)	160.00	$17.00	$2,720.00
Physicians	2.50	$75.00	$187.50
Totals	295.83		$5,174.17

Over a two-year period, the total number of patients and next-of-kin that will be completing the questionnaire are 880 (1100 cases-220 cases in the pilot study) and an additional 20 physicians and experienced medical staff will complete the abstraction forms for the medical history and pathology records. The annualized burden for the respondents is estimated at 296 hours (Table A.12-1). Based on these estimates, the annualized costs to the respondents will be $5,174 (Table A.12-2).

A.13 Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There is no additional annual cost burden to respondents or record keepers for capital or start-up costs, or for operation, maintenance, or purchase of services. All infrastructure remains available from the previous case-control study.

A.14 Annualized Cost to the Federal Government

Annual costs will provide IARC with funding for the principal investigators in each of the 6 study centers. This fee will cover payment for the physician abstractors and interviewers. NCI staff time will be used to carry out planning and design activities, monitor contractor work, and provide pathology expertise ($80,000 per year). Non NCI contractors and collaborators will be required for study support and some areas of expertise as needed. Therefore the total bi-annual costs are shown in Table 14.1, below. The total annualized cost to the Federal Government is estimated at $164,880. Over the course of the two years of data collection the total cost to the Federal Government is estimated $329,760. These figures include direct and indirect costs.

Table A.14 - 1 Annualized Costs To the Federal Government			
	Labor Hours	Wage Rate	Total Cost
Merging Data IMS	500	$50/hour	$25,000
IARC Staff	1097	$40/hour	$43,880
TOTAL CONTRACTOR COST			
NCI Staff	1600	$50/hour	$80,000
Other Costs including: Travel of Staff to Annual Meeting			$4,000
Equipment Costs			$5,000
Editing, Coding, Tabulation and Analyses of Data			$5,000
Publication of Results			$2,000
TOTAL ANNUAL COST			$164,880

A.15 Explanation for Program Changes or Adjustments

This is a new collection of data.

A.16 Plans for Tabulation and Publication and Project Time Schedule

Data will be received at IARC (Lyon, France) from each center and will be forwarded to the NCI. Statistical analysis will be performed, using SAS 9 software. Survival time (from diagnosis to death or to end of follow-up) will be calculated for each patient. Survival will be compared using the log-rank test to evaluate the Kaplan-Meier survival distributions. The Cox model will be used to analyze the impact of prognostic factors, including age, sex, tobacco smoking, genotype variation, treatment, tumor histology, and tumor marker variation. The Standardized Incidence Ratios (SIR) and 95% CI for second primary tumor (SPT) will be calculated using Eurocare rates for expected number of cancer computations.

The main outcome of this study will be used to compare the number of RCC deaths vs. censoring (those alive at 5-years, those lost to follow-up, those that died of other causes). The four outcomes we intend to evaluate specifically include: a) RCC death; b) Alive: disease recurrence (same clinical stage or disease independent of primary tumor) c) Alive: disease progression (disease presents at higher clinical stage than primary diagnosis) d) Censored (alive at 5-years, lost to follow-up, died of other causes). As in the case-control study, physicians and experienced medical staff will be employed to abstract hospital records, pathology reports and treatment information. After we distinguish the types of follow-up protocols used and procedures followed in each country, we will develop a definition of those cases confirmed to be disease-free (using "high-confidence methods, i.e., CT, PET, laboratory methods, other), and patients for whom follow-up was not confirmed, incomplete, or undetermined ("low confidence confirmation"), so that we can stratify by this variable and conduct restricted analyses. We plan to collect information on methods used to evaluate disease status. Treatment variables will be grouped into broad categories. These new groups will be used as adjustment variables. Lastly, we will initiate follow-up at date of diagnosis and collect survival at 5-years, controlling for treatment and perhaps with time dependent co-variables for treatment duration as needed. We will not discount any time during cancer treatment towards survival as this could make more advanced cases with longer treatment duration incorrectly appear to have a longer disease-free survival.

Publications addressing all of the above topics will be submitted to appropriate scientific journals. A steady stream of publications has been generated from the case-control study and any of the molecular markers of genetic susceptibility and tumor heterogeneity that were analyzed in relation to risk factors will now be analyzed in relation to survival status. To date 12 papers have been published or have been submitted for publication (Attachment 1), at least 15 more are in preparation.

The project time schedule for the pilot study and main study are provided below (Table A.16-1). During the pilot study we will interview next of kin for 9 cases and 220 patients (NIH Clinical Exemption #CE 08-05-01). After we have received OMB approval, depending on the results of the pilot study, we will proceed with the survival study data collection, analysis and publications.

Table A.16-1 Project Time Schedule Pilot study (pre-) and Survival Study (post-OMB approval)

	Months after OMB approval			
	Month 1-9	Month 9-11	Months12-26	Months 24-36
Pilot Study Data Collection (N=220)				
Pilot Study Statistical Analysis				
Survival Study Data Collection (N=880)				
Survival Study Statistical Analysis				
Summarize and Publish Results				

A.17 Reason(s) Display of OMB Expiration Date is Inappropriate

This study will display the expiration date for OMB approval of the information collection.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions

The Follow-up of Kidney Cancer Patients from the Central European Multicenter Case-Control Study will comply with 5 CFR 1320.9, the Certification for Paperwork Reduction Act Submissions.