

Supporting Statement B for:

**A multi-center international hospital-based case-control study of
lymphoma in Asia (AsiaLymph) (NCI)**

February 22, 2012

Submitted by:

Occupational and Environmental Epidemiology Branch
Epidemiology and Biostatistics Program
Division of Cancer Epidemiology and Genetics (DCEG)
National Cancer Institute
National Institutes of Health
Rockville, Maryland 20852

Contact Person: Nathaniel Rothman, M.D., M.P.H., M.H.S.
NCI Project Officer
Executive Plaza South, Room 8118
NCI/NIH EPS 8116
Bethesda, MD 20892

Phone: (301) 496-9093
FAX: (301) 402-1819
e-mail: rothmann@mail.nih.gov

TABLE OF CONTENTS

B. STATISTICAL METHODS

B.1	Respondent Universe and Sampling Methods.....	1
B.2	Procedures for the Collection of Information.....	4
B.3	Methods to Maximize Response Rates and Deal with Nonresponse.....	7
B.4	Tests of Procedures or Methods to be Undertaken.....	7
B.5	Individuals Consulted on Statistical Aspects and Individuals Collection and/or Analyzing Data.....	8

LIST OF ATTACHMENTS

- Attachment 1. Protocol including bibliography
- Attachment 2. List of Consultants
- Attachment 3. Screener and Core Questionnaire
- Attachment 4. Occupational Job Exposure Modules - examples
- Attachment 5. Occupational Job Exposure Modules – complete set
- Attachments 6A to 6E. Institutional Review Board (IRB) Approvals
 - 6A: National Cancer Institute Special Studies and NIH IRB review
 - 6B: Hong Kong University – Study Coordinating Center and Coordinating Center for Hong Kong IRB review
 - 6C1: Sichuan University Huaxi Hospital – Study Coordinating Center for Chengdu IRB review in original language;
 - 6C2: Sichuan University Huaxi Hospital – Study Coordinating Center for Chengdu IRB review in English language;
 - 6D1: Tianjin Medical University Cancer Institute and Hospital – Study Coordinating Center for Tianjin IRB review in original language;
 - 6D2: Tianjin Medical University Cancer Institute and Hospital – Study Coordinating Center for Tianjin IRB review in English language;
 - 6E1: Dalin Tsu-Chi General Hospital – Study Coordinating Center for Taiwan IRB review in original language.
 - 6E2: Dalin Tsu-Chi General Hospital – Study Coordinating Center for Taiwan IRB Review in English language.
- Attachment 7. Subject Contact and Consent Form
- Attachment 8. Administrative form for the Pathologist
- Attachment 9. Administrative forms for the Interviewer
- Attachment 10. AsiaLymph Study Organization

B. STATISTICAL METHODS

B.1 Respondent Universe and Sampling Methods

We are conducting a hospital-based case-control study. Our goal has been to conduct the study in several regions of Asia to:

- increase variability in exposure to key risk factors;
- have enough study centers and hospitals to be able to enroll 3,300 lymphoma cases and 3,300 controls in three years;
- have a number of centers with a high prevalence of exposure to occupational compounds of interest; and,
- the extent possible, to carry out the study in centers and regions where NCI personnel have successfully carried out research previously and to be able to take advantage of existing infrastructure and experience.

The AsiaLymph study organization consists of two Study Coordinating Centers (University of Hong Kong and Queen Elizabeth Hospital), four Study Centers with responsibility for all study subject contact and 20 Hospitals (**Attachment 10**). Centers were considered for inclusion in AsiaLymph based initially on NCI study personnel's familiarity with a particular site, additional information provided through lymphoma and hematological pathologists and clinicians identified through literature searches and through contacts we have had through the course of other research conducted in Asia; and a literature search to identify investigators who had carried out any type of study of lymphoma previously in this region.

Additional issues taken into account were as follows:

- 1) Availability of local industrial hygienists and occupational health personnel to work with us on the exposure assessment effort;

- 2) Availability of local epidemiologists in each center;
- 3) Availability of high quality lymphoma pathologists in a given hospital;
- 4) Willingness to collaborate with other hospitals in a given center;
- 5) Willingness to collaborate with NCI on a large, multi-centered effort that required shipment of blood samples to NCI, and shipment of tumor samples to Hong Kong for central pathology review and to NCI for molecular analyses.

We identified four centers (**Attachment 1**) that fulfilled all criteria and in the aggregate allow us to accomplish the scientific objectives of AsiaLymph. Within each center, the hospitals that will be participating in the study see approximately 75-95% of all lymphoma cases in their geographical region and include all major hospitals. Hospitals that were excluded from the study were small hospitals in these regions and often did not fulfill one or more criteria listed above.

Eligible cases will be Chinese patients at a participating hospital who are between 18 and 79 years of age at time of initial diagnosis and admitted or treated with incident diagnoses of any lymphoid neoplasm. An incident case will be defined as a case enrolled into the study within 12 weeks after the date of diagnosis of a lymphoid neoplasm. Cases will be permanent residents of the general geographic region that is served by the hospital at the time of diagnosis. Specifically, they must have lived in this general geographic region for at least 15 years at some time in the past. Cases with a previous diagnosis of lymphoma are ineligible. A rapid case ascertainment system will be established for case identification in participating hospitals in order to identify and approach all eligible cases. If a case is missed from enrollment during the initial visit to the hospital, the case will be approached at the next scheduled follow-up visit to the hospital. A case referred from a non-study hospital/clinic to a study hospital will be eligible for inclusion into the study, if they come from the general geographic region served by the study hospital, if they are

enrolled at the study hospital within 12 weeks of diagnosis, and are otherwise eligible for the study based on the same criteria used for patients initially seen at a study hospital.

Controls will be enrolled from Chinese patients seen at the participating hospitals. Controls will be individually matched to cases by hospital, age at date of diagnosis/admission (+/-5 years), sex, and date of admission (within 3 months). Further, all cases and controls must live in the same general geographic region served by the hospital and have lived in this region at least 15 years at some time in the past. Controls will be drawn from patients seen at the same hospital for diseases/conditions that are unlikely to be associated with risk factors under study, such as injuries and selected diseases of the circulatory, digestive, genitourinary, and central nervous system (**Attachment 1**). Each potential control disease has the same general referral pattern as lymphoma cases to avoid bias. Patients with a history of any lymphoma, including acute lymphoblastic lymphoma, multiple myeloma, chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma, will not be eligible to serve as controls.

The interviewer in each hospital will randomly select one of the five disease categories from which to draw a given potential control patient for a specific case. The interviewer will then identify potential controls from admissions records with a disease from one of the five disease categories who could be a match to a given case on age and sex, randomly select one control patient from the list of potential matched controls, and approach the potential control patient, explain the study, and obtain information to determine if the patient is eligible (i.e., residence in the current geographic region for at least 15 years in the past and no prior history of a lymphoid neoplasm). If the patient is not eligible, or the patient is eligible but does not consent to participate in the study, then the interviewer will randomly select another potential control from

the list of potential matched controls (**Attachment 1**). No more than ~15% of controls enrolled in any hospital will have one type of control disease.

B.2 Procedures for the Collection of Information

Both cases and controls will be interviewed within 48 hours after they are identified. A computer assisted personal interview (CAPI) will ascertain occupational, family, medical, lifestyle, and residential histories (**Attachment 3**). The CAPI will trigger occupational exposure assessment modules in the OccIdeas system designed specifically to assess occupational exposures using more detailed, exposure-oriented job and industry questions. Specifically, a patient who reports a particular combination of industry and job title will trigger questions for certain types of occupational industries, job titles, or types of chemical exposures (e.g., benzene, trichloroethylene) (examples in **Attachments 4 and 5**). A key feature of the OccIDEAS system is the ability to program exposure decision rules based on the patterns of responses to one or more questions, which provides automated exposure assessments and substantially reduces the time and expense needed to publish occupational data collected a given study. We estimate that about 50% of study subjects will be administered 1-3 of these modules and that the remaining 50% will not be administered any modules.

In addition, interviewers will scan selected documents from the medical record (e.g., discharge summary, pathology report, major diagnostic tests) for use in confirming case diagnosis, which will be conducted through a central pathology review by the study pathology center in Hong Kong. Interviewers will upload the CAPI, which will be automatically encrypted, and scanned files to the study coordinating center (Hong Kong University School of Public Health). Interviewers will use various tracking forms to ensure that all study activities are completed (**Attachment 9**).

A 27 ml blood sample will be collected from each study subject. To the extent possible, blood samples will be collected prior to initiation of therapy. The samples will be collected in EDTA vacutainers (3 tubes with 9 ml each). The samples will need to be transported to the processing laboratory within 4 hours and processed, which will include standard low speed centrifugation, vortexing, and aliquotting into 1ml plasma aliquots and the remaining blood fraction into 3.4 ml aliquots. Aliquots will then be stored at either -20°C short-term for up to one week and then stored at -80°C, or stored at -80°C immediately after aliquotting. Information about biologic sample collection, processing, aliquotting and storage. The processed samples will be shipped to the study center and subsequently the NCI biorepository, where they will be stored at -80 °C until they are used up. The NCI SSIRB has explicitly requested that this language be used and that a time limit for storing samples not be used in the study or in the informed consent.

A buccal cell sample will be collected and used as an additional source of DNA and for viral studies. Buccal cells will be collected from cases and controls by swishing water in mouth for about a minute. Isopropanol will be added to the sample, which will then be centrifuged, the supernatant removed, and cells frozen. The pellet will be stored at -20 °C, and samples will subsequently be shipped to the study center followed by the NCI Repository and stored at -80°C. Tumor tissues, including pathology blocks for review, diagnosis, and molecular typing, and snap frozen tissues will be collected where possible. For each case, 25 unstained 5 micron sections on HistoBond slides will be made and shipped to the study pathology center. The 25 unstained sections will be cut and mounted on the HistoBond slides. Two 20 µm-thick sections will also be cut and placed in two separate eppendorfs for molecular studies.

Evidence increasingly supports both commonality and heterogeneity in the etiology of lymphoid neoplasms. It is therefore essential that an epidemiologic study of lymphoid neoplasms

achieve high quality diagnostic specificity in identifying disease subtypes. Classification of lymphoid neoplasms has evolved rapidly in recent decades. In 2001, the World Health Organization (WHO) introduced a new classification that was adopted worldwide and represents the current gold standard for classifying all hematopoietic neoplasms (Jaffe et al. 2004; Swerdlow 2009). Because of variability in the laboratory testing undertaken, additional immunophenotyping is often required in order to achieve high confidence in the diagnosis (Turner et al. 2004). Based on the importance of accurately identifying lymphoid neoplasms and classifying disease subtypes, AsiaLymph will conduct centralized pathology review for all cases using the gold-standard WHO classification. The pathology review will take place in Hong Kong, led by Dr. John Chan, an internationally-recognized expert hematopathologist.

The study team has had extensive experience conducting multi-center studies and have used the experience acquired from these previous investigations to design the quality control component of the study. Site-visits will be conducted to every study center and hospital by coordinating center staff to review all aspects of the study. NCI staff will visit each center and hospital every 6 months. In addition to the oversight of the study in Asia, NCI staff will review the study status on a weekly basis, including review of enrollment reports generated from the study management system in Hong Kong, review of questionnaires for completeness and quality, and review of biological sample collection, processing and storage. NCI staff will also have a weekly phone call with the coordinating center to review all aspects of the study. A study management system (SMS) with online access will track subject enrollment, interview and hospital record status, biospecimen and tumor tissue collection status, and other key data as described in the protocol. The SMS must be available to study staff at the Study Centers for data input and reporting, and to NCI investigators to monitor study progress.

B.3 Methods to Maximize Response Rates and Deal with Nonresponse

Based on the relatively high participation rates we have had in previous types of studies in Asia, we expect to have a participation rate between from 70% - 85%. We will spend a substantial amount of time during training on approaches to enhance patient participation and refusal conversion. Further, we will closely follow case capture rates, case and control participation rates, and pre-treatment phlebotomy rates and identify hospitals and interviewers that are low outliers and re-train as needed.

B.4 Test of Procedures or Methods to be Undertaken

The questionnaire used in AsiaLymph represents the cumulated experience obtained in multiple case-control studies of cancer conducted by DCEG epidemiologists who are working on AsiaLymph, including studies in Asia, Europe, and the United States. Many questions are in a standard format that has been used in other studies. Some represent revisions made to such questions based on the experience obtained in previous studies. In addition, the procedures for the collection and processing of biologic samples are standard and have been used successfully in previous studies. Further, we have conducted a pilot test of the AsiaLymph questionnaire and study procedures on 9 subjects and that experience has been used to revise the questionnaire.

Finally, the first month of the full study, scheduled to take place in March, 2012, will be considered an additional pilot test of the questionnaire and revisions may be made after that time, which would result in rephrasing a few questions and/or eliminating a few questions. Overall, if the questionnaire is revised, it would result in a reduction of time required for its administration.

B.5 Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

The Biostatistics Branch of the NCI Division of Cancer Epidemiology and Genetics (DCEG) has a staff of biostatisticians who are experts in this type of study. Dr. Sholom Wacholder, Senior Investigator, is a member of this branch and the study lead investigator for study design/statistical analysis. Further, Dr. Nilanjan Chatterjee, Chief of the DCEG Biostatistics Branch, is a study co-investigator. The statistical analysis plan and power calculations were developed with these investigators and are provided in the protocol (**Attachment 1**).

The study centers in Hong Kong, Chengdu, Tianjin, and Taiwan are responsible for data collection activities under this protocol (**Attachment 1**). The study organization and list of key non-Federal personnel for the study is shown in **Attachment 10**.

The National Cancer Institute is responsible for overall study management and coordination and statistical analysis. Federal scientific investigators conducting data analysis are listed in **Attachment 2**.