

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

The Multicenter Hemophilia Cohort Study

A handwritten signature in black ink, appearing to read 'Elias A. Zerhouni', written over a horizontal line.

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## The Multicenter Hemophilia Cohort Study

### Introduction

In their reports on the Fiscal Year 2006 budget for the Department of Health and Human Services, the House and Senate Committees on Appropriations stated:

“The Committee understands that field work on the Multi-Center Hemophilia Cohort Study will be complete in September, 2005. This cohort offers a rich database for improving the understanding of hepatitis C virus and other concerns of major public health interest. The Committee expects NCI to take all necessary steps to ensure the samples obtained through this cohort are preserved and accessible for future research. The Committee also requests a report by March 31, 2006 on possible future research opportunities using the cohort samples.” (House report No. 109-143, page 60.)

“The Committee understands that NCI has made plans to discontinue research funding support of the Multi-Center Hemophilia Cohort Study. This cohort offers a database for improving the understanding of HCV and has served as the basis of significant peer-reviewed findings. The Committee strongly urges the NCI to take all necessary steps to ensure the samples obtained through this cohort are preserved and accessible for future research. The Committee also requests a report by May 1, 2006 on possible future research opportunities using the cohort samples.” (Senate report No.109-103 page 92-93.)

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to these requests.

### Background

Shortly after acquired immunodeficiency syndrome (AIDS) was identified in 1981, it soon became apparent that persons with hemophilia were also affected by the disease. Persons with hemophilia were at especially high risk for human immunodeficiency virus type 1 (HIV-1) infection because of their need for infusions of blood clotting factors derived from the plasma of thousands of donors. It was also widely accepted that virtually all persons with hemophilia who had been exposed to non-heat treated factor concentrates had already been infected with hepatitis B and hepatitis C. In 1982, intramural investigators from the National Cancer Institute (NCI) initiated a series of studies collectively known

as the first Multicenter Hemophilia Cohort Study (MHCS-I). The study was designed to address emergent clinical and epidemiological issues associated with hemophilia and viral infections, including the transmission of HIV-1 and disease progression to AIDS. The study incorporated twelve comprehensive hemophilia centers throughout the U.S. and Europe.

Over the course of MHCS-I, several important discoveries were made. Since the cohort was highly representative of the total population of hemophilic patients in the U.S., one of the most pivotal discoveries was that second to AIDS, liver failure was a leading cause of death among this group. Further studies demonstrated that an HIV-related immune deficiency was strongly associated with increasing hepatitis C virus (HCV) load, that individuals infected with HCV had a higher risk of liver-related complications (end stage liver disease, enlarged liver, and liver failure) than those not infected, and that those co-infected with HCV and HIV viruses had an even higher risk.

As the focus of research increasingly shifted to the natural history of HCV and the identification of factors that affected the risk of disease complications of HCV and HIV in persons with hemophilia, the MHCS-I closed in 1999 to allow for a larger study with 54 hemophilia centers in 8 countries. The new study, called the MHCS-II, was co-sponsored by the National Heart, Lung and Blood Institute (NHLBI) and NCI, and designed to further investigate viral co-infection, disease progression, predictive markers for AIDS and liver disease, factors that affect prognosis, genetic susceptibility to infection and disease, including opportunistic infections and cancers that arise excessively in persons with hemophilia. In particular, investigators sought to ascertain the incidence of liver decompensation, hepatocellular carcinoma, and non-Hodgkin lymphoma.

Consenting participants, who were hemophilic patients with HCV with or without HIV co-infection, provided blood and urine specimens upon enrollment and annually thereafter for 3-to-4 years. After preliminary analysis, remaining blood specimens were frozen and sent to a central repository for storage. Residual tissue specimens from the liver, lymph nodes, or other tissues suspected or known to be malignant were collected from biopsies or resections that had been performed for clinical indications and sent to the central repository for later analysis.

#### Accomplishments and Plans

Together, the MHCS-I and -II have served as a rich and important resource for the study of the prevalence of HIV-1 and HCV infection among a large proportion of

persons with hemophilia. To date, the repository holds over 27,000 biological specimens, including lymphocytes, plasma, and serum from more than 2,500 individuals. All of these patients are HCV-positive, and nearly three-quarters of them are also HIV-positive.

Biologic specimens from the MHCS continue to be uniquely valuable for future research on HCV infection and other diseases of major public health interest. Following completion of field work on the MHCS in 2005, the data and specimens collected since 1982 will continue to be safely and securely maintained by NCI in biorepositories and databanks where they will be accessible to the research community for the foreseeable future.

NCI requires that its biorepositories follow rigorous procedures for biospecimen storage and handling. Strict quality control guidelines for specimen tracking, inventory, shipping, temperature monitoring, and security are in place to ensure the highest standard of preservation for all specimens. Computerized record systems maintain vital data permitted under the Federalwide Assurance terms, including vial location, quantity, and processing history. Each vial stored within the facility is tagged with the relevant data, and the record systems also monitor incoming and outgoing shipments. State-of-the art temperature monitoring systems constantly maintain controlled storage conditions and trigger an immediate personnel and energy-backup response if a system failure or breach occurs.

NCI will ensure and maintain the quality of the MHCS data, assemble data sets, and post them at the study website <http://dceg.cancer.gov/mhcs-ii>. The publicly accessible website will be updated in 2006 to include basic demographic information and standard virologic and clinical results from the MHCS. In addition, the website will include menu-directed procedures for on-line data analysis and for generating inventories of the biologic specimens from the cohort that are stored at the repository.

It is anticipated that there will be a wealth of future research opportunities involving the use of the cohort specimens, including studies of risk factors, prognosis, and outcomes for persons with hemophilia, including those who develop HIV or HCV infections, hepatocellular carcinoma, lymphoma, and other related conditions. Other potential areas of research include predictive markers for AIDS or liver disease, factors that affect genetic susceptibility to infection and disease, as well as the incidence and natural history of opportunistic infections and cancers that affect persons with hemophilia.

Applications for use of MHCS specimens will be reviewed by a Specimen Resource Facilitation Committee, with additional expertise provided by ad hoc reviewers for specific proposals, as necessary. All applications will be required to include the background and rationale of the proposed investigation, performance characteristics of the proposed assays, technical specifications of the specimens, and a list of the particular specimens requested. Criteria for approval of requests for specimens will include scientific merit, appropriate Institutional Review Board approvals, quantity of specimens available at the time of the application, and overlap with previously approved projects. In most instances, a decision may be expected within two months of receipt of the application. Successful applicants, upon completion of testing and publication in the scientific peer reviewed literature, will be required to submit their final results to NCI for addition to the MHCS public website.

### Conclusion

The MHCS data and repository specimens will continue to serve as a unique and valuable resource for future research investigations. NCI is committed to providing both online public access to MHCS data and procedures for analysis of MHCS specimens. Likewise, NCI, in consultation with NHLBI, will assure the integrity of the specimens and procedures to maximize the likelihood that these specimens will be used to substantially advance scientific knowledge. The publicly available data and the procedures for obtaining specimens should facilitate investigators in developing applications for NIH grants and other support mechanisms. Ultimately, this important resource will lead to advances in clinical research to improve the health and care of hemophilia patients, particularly those affected by HCV and HIV.