

## PROTOCOL

**Title:** Universal Data and Serum Specimen Collection (UDC) System for Hemophilia.

### **Description**

The primary congenital bleeding disorders are hemophilia A and B, which affect approximately 1 in 5,000 males and von Willebrand's Disease which affects 1 in 100 men and women. Several plasma proteins called factors are necessary for normal blood clotting. Persons with hemophilia are either missing a particular factor in their blood that is essential to the clotting process or the protein is present but does not work. Without this factor, bleeding into muscles, joints, and internal organs often occurs without any noticeable trauma. The treatment of a bleeding episode involves the replacement of the missing protein through the intravenous administration of factor concentrate which is derived from, or contains components of human blood plasma. The frequent bleeding and secondarily, the necessary intravenous administration of blood products to control this bleeding, are responsible for the two most severe complications of hemophilia which are: 1) the development of chronic, and often debilitating joint disease from repeated bleeding into major joints such as the knee and ankle; and, 2) infection with viral, blood-borne diseases such as hepatitis and human immunodeficiency virus (HIV) that can be transmitted in the blood products.

About three-fourths of all persons with hemophilia in the U.S. receive at least some of their medical care from federally-sponsored, specialized hemophilia treatment centers (HTCs) located throughout the country. These centers currently provide care to over 27,000 children and adults with these disorders. For years, the Division of Hereditary Blood Disorders of the National Center for Infectious Diseases, Centers for Disease Control & Prevention (CDC) has provided support to these treatment centers for programs designed to prevent complications of these disorders.

The Universal Data and Serum Specimen Collection (UDC) System will extend CDC's collaboration with the HTCs by assisting with the analysis of a uniform set of clinical data routinely collected by HTCs. These data are used to monitor the extent of complications of congenital bleeding disorders in the U.S. Specific measurements will be analyzed to evaluate the degree of joint disease. In addition, free testing of serum specimens collected annually from persons receiving care in the HTCs for the presence of blood borne pathogens will be offered by CDC to assist HTCs in monitoring related infections. After testing, the remainder of each serum specimen will be used by the CDC to establish a serum bank for possible future use in evaluating the safety of blood products used by these persons. Information from this system will be used by the Division of Hereditary Blood Disorders of the CDC to assess the safety of the blood supply and to develop and monitor the effectiveness of interventions designed to address our mandate from Congress which is to reduce or prevent the complications of hemophilia. It is anticipated that the Universal Data and Serum Specimen Collection System will continue into the foreseeable future as the CDC continues its prevention activities for this population.

**Project Director**

J. Michael Soucie, Ph.D., Epidemiologist, Division of Hereditary Blood Disorders - Dr. Soucie will coordinate the development of the data collection instruments, provide technical assistance related to the collection of data, and will conduct the analyses and generate reports from the data.

**Methods and Materials*****Data Collection***

The CDC has entered into a five-year cooperative agreement with HTC's in the U.S. to provide health related services directed toward the reduction or prevention of the complications of hemophilia. As part of this agreement, the CDC will provide resources and technical assistance to staff at the HTC's to facilitate their efforts in collecting clinical data.

All persons with hemophilia A or B and related disorders who receive care at an HTC are eligible for inclusion in the data collection effort. Routine clinical data will be collected using a combination of medical record abstraction or direct patient interview by HTC staff as a part of the routine clinical assessment. Information will be recorded on standardized data collection forms. There are two parts to the data collection: patient registration and current clinical information recording. The Registration Form is completed one time only for each patient and serves to introduce the patient into the data system. Data collected on this form includes baseline demographic and clinical information that does not change over time. The current clinical information is collected by using the Annual Form for participants 2 years old and older, and by using the Baby Visit Form for children under two years old. The Annual Form is completed for each patient  $\geq 2$  years old by treatment center staff at the first visit and once per year thereafter and collects detailed information on clinical outcomes concerning joint disease and viral and other complications. The Baby Visit Form is completed by treatment center staff at the first visit and at 6 month intervals until age 2 years. The Baby Visit Form collects information on current treatment, bleed history, and clinical outcomes. In addition, patients may be asked to complete standardized and validated age-appropriate quality of life instruments as part of the study.

Completed data collection forms will be regularly entered into computer software by trained personnel at CDC. The software is designed to perform reliability checks on the entered data and reduce the likelihood of data entry errors by using a double entry system. The software automatically generates several reports for use in compliance and quality assurance including: 1) a report of items that failed reliability tests that need correction or verification from the HTC; 2) a report that lists all collection forms entered into the system and whether the forms passed or failed reliability checks; and 3) a report that details the time from initial data entry to when the collection form passes all reliability checks to assess the timeliness with which the HTC's provide correction and verification information. The processed data will be provided to HTC's for their use in monitoring prevention interventions.

The HTC network has supported the development of a clinical database software tool with the capacity to validate and store the data collected for UDC. CDC has provided specifications for electronic storage and transmission of UDC data to CDC using established protocols for data integrity and security. An HTC may choose to enter their data into this tool for validation and electronic transmission to CDC. A copy of the transmitted data is also stored at the local data entry site for archival purposes and to allow re-transmission of data if technical problems with a previous transmission make this necessary.

### ***Serum Testing & Storage***

Treatment of persons with hemophilia and related disorders often involves infusion of blood products which may be contaminated with blood-borne viruses. Despite the risk of infection, many patients are not routinely tested for exposure to these agents, due largely to non-medical factors such as lack of adequate or appropriate insurance coverage. It is also possible that exposure to unknown viruses or to viruses undetectable with current technology may occur.

Therefore, so that information about the occurrence of blood-borne, viral diseases can be universally and uniformly collected, patients will be asked to voluntarily provide a serum specimen annually that will be tested centrally for the presence of hepatitis A, B, and C viruses, human immunodeficiency virus (HIV), or other blood borne viruses. The remainder of the blood specimen will be stored for future testing, as needed, for the detection of viruses, diseases or conditions of particular importance to persons with hemophilia. All participants will receive pre- and post-test counseling regarding the implications of infection with hepatitis and/or HIV from staff at the HTC as has been the usual practice.

Specimens will be prepared according to guidelines provided by CDC and mailed using appropriate packaging to the CDC Serum Bank and Epidemic Response Laboratory located in Lawrenceville, GA. Specimens will be processed and allocated as follows: one portion will be stored; one portion will be used for hepatitis testing according to an algorithm provided by CDC that is based both on the results of previous testing and on current evaluation standards and practices; for persons who have not had a previous positive HIV test, a portion will be used for HIV antibody testing; any remaining serum will be stored. Testing will be performed in CDC laboratories and/or in external laboratories as necessary. If a specimen is sent to an external laboratory, the data accompanying the specimen are the specimen number and the CDC ID number. Information about vaccination status and the results of previous viral testing performed at the HTCs will be collected and used to determine the need for further testing. CDC will continue to recommend vaccination of patients susceptible to hepatitis A and B.

The results of viral testing will be sent in hard-copy format to the HTC sending the specimen so that the results can be reported to the patient. In addition, the results will be input into the central database for storage and further analysis.

### ***Data Analysis & Reporting***

Analyses of the data collected from medical records and patient interview will be performed on a

regular basis to provide summary data to HTC's as needed. It will also be used to guide programmatic activities of the Branch. These analyses will consist primarily of descriptive reports detailing the occurrence rates of complications among subgroups of persons defined by demographic, geographic, and clinical characteristics. The primary purpose of these analyses will be to define subgroups of the population at high risk for complications so that interventions can be targeted toward these groups.

Reports of these descriptive analyses will be prepared annually for dissemination on a regional basis throughout the country. These reports will also contain information about CDC program activities relating to these data. In addition, data will be made available to regional coordinators for use in evaluating regional prevention activities.

Analyses of the results of serum testing for viral infections will be performed monthly. During the first year of the project, analyses will yield prevalence rates of infection and hepatitis vaccination in the population. Test results obtained on the same patients in subsequent years will be used to calculate incidence rates of seroconversion. These analyses will be descriptive in nature and will focus on highlighting demographic and geographic variability of rates. Trends in these rates will be monitored continuously using analyses and reports similar to those used to track reportable conditions in the MMWR. These analyses and reports will be disseminated to the treatment centers in a timely manner. Increases in rates of infections over a predetermined threshold will prompt investigations into the cause with specific attention paid to blood safety issues.

### **Followup Investigations**

Infections among individuals using blood products may be indicators of a blood safety problem. Immediate investigation of these events is important so that the source can be identified and interventions can be applied to prevent further spread of the infection into the population. As part of these investigations, CDC may request assistance from treatment center staff to obtain additional clinical specimens (e.g., repeat serum specimens, stool samples, implicated blood product samples) and risk factor information (e.g., blood product exposure histories).

### **Participants**

All persons with hemophilia and related clotting disorders in the U.S. who use federally-supported comprehensive hemophilia treatment centers for at least some of their care will be eligible for participation. Participants will be enrolled by staff at the treatment centers who will explain the nature and purpose of the project and obtain informed consent for participation.

### **Risks & Benefits**

There may be some discomfort to patients associated with the withdrawal of blood samples. Occasionally, there is some bruising, and very rarely an infection may occur. It will take

approximately 10 minutes to answer the questions about health-related matters.

The potential benefits to patients include the knowledge of whether or not they have been exposed to hepatitis or human immunodeficiency viruses. Patients who have been infected with a virus will be identified and counseled by their physician about the significance of this. The detection of infection by blood test is important because persons with these viruses may have few, if any, symptoms. Early detection of viral infections can help physicians better plan the future care of their patients. Finding the source of the infection can help to prevent the virus from further spread to others. Patients who have a negative blood test for viruses will benefit by being reassured that they are not infected. In addition, the establishment of a national serum bank will permit the evaluation of potential threats to blood product safety in the future as new diseases of clinical importance are discovered and tests become available. For example, the existence of such a resource in the early 1980s may have led to earlier recognition of the transmissibility of HIV through blood products and resulted in decreased exposure in the hemophilia community.

### **Informed Consent Procedures**

Informed consent will be obtained from all patients by HTC staff prior to collection of any data or blood specimens. Children's assent will be obtained from children 7 years of age or older. Planned site visits conducted by CDC staff will include procedures to ensure that informed consent has been obtained and that appropriate documentation is present in patient medical records.

### **Records Management**

Data will be collected on standardized forms developed by HTCs with technical assistance from the CDC. Standardized forms will be made available to all participating centers. The forms will be completed in duplicate: one copy will be retained at the HTC; the second will be mailed to CDC for electronic data entry and validation. HTCs using a clinical software tool to collect and store UDC data utilize established methods to protect these data including computer password protection that is in compliance with HIPPA standards and scheduled data backup. A unique identifying code will be assigned to protect patient confidentiality. Sensitive information regarding sexual practices of patients who are infected with HIV is required to evaluate programmatic activities regarding HIV risk reduction.

### **Assurances of Confidentiality**

All data and serum specimens sent to CDC will be identified with a unique code based on the Soundex system that will be known only to treatment center staff. No personal identifiers will be sent to CDC. All results of data analyses will report group data and care will be taken to assure that individual patients cannot be identified. Confidentiality of all records and materials will be guarded to the fullest extent possible. The signed consent forms will be kept in locked files at

the HTCs. No personal identifying information will be contained in the records maintained at the CDC. In addition, these records will be stored at CDC in locked file cabinets, computer files with this information will be password protected, and documents with this information will be shredded when ready for disposal. Information obtained from this study may be published in the medical literature. However, no information will be disclosed that might result in identification of any individual participant. The CDC or their designate may inspect the records relating to participant's involvement in the study.