



Michigan Blood Safety Surveillance among People with Blood Disorders Study Protocol

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Title of Study: Michigan Blood Safety Surveillance among Persons with Blood Disorders

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I. Background and Purpose

Blood transfusions are the foundation of care for patients with sickle cell disease and thalassemia. Consequently, transfusions can be a major source of complications for these conditions. Because there is no natural way for the body to eliminate iron, the iron in the transfused blood cells builds up and becomes toxic to tissues and organs, particularly the liver and heart. Iron overload is a severe complication of transfusions that can result in early death from organ failure. Frequent blood transfusions also expose people to infections that may be transmitted through blood. Although blood donors are screened for a number of known infectious diseases, it is possible that new infectious agents or those previously not recognized as blood transmissible would be missed by this screening. The risk of transmitting infection through blood transfusion has been greatly reduced as a result of increased vigilance in donor screening and the increasing sensitivity of laboratory screening tests, however, substantial risks of blood transfusion-related mortality that are non-infectious complications (e.g., transfusion-related acute lung injury [TRALI]), acute hemolytic transfusion reaction, and subsequent iron-overload from repeated transfusions) persist. Additionally, patients with rare blood phenotypes are at higher risk for alloimmunization, increasing the risk of adverse transfusion events.

The Michigan Department of Community Health is working on a new project with the Centers for Disease Control and Prevention (CDC) in collaboration with four Michigan clinical facilities: University of Michigan Health System, Michigan State University, Detroit Receiving Hospital (Detroit Medical Center), and Children's Hospital of Michigan. The purpose of this overall project is to monitor the safety of the nation's blood supply and meet the shifting priorities of blood safety within heavily transfused patient populations. This program will involve ongoing collection and analysis of health-related data and biospecimens to monitor the frequency of different diseases and health conditions within this population. Data generated from this program will be used to manage future public health programs specific to this population. The intended benefits of the project are primarily or exclusively for the participants. It is therefore designated a non-research program by the CDC.

Study Objectives

Outcomes for this surveillance project include the following:

- 1) A better understanding of the risks related to transfusion complications and infectious transmissions
- 2) An annual laboratory analysis of specimens to determine the burden and location of transfusion-transmitted emerging pathogens
- 3) A better understanding of rare blood types and blood banking practices
- 4) Monitoring the rates of transfusion-related complications
- 5) Development of interventions to prevent the complications of chronic transfusion



II. Summary of Procedures

Serum Testing & Storage

Treatment of persons with some blood disorders involves frequent transfusion of blood, which may be contaminated with blood-borne pathogens. It is also possible that exposure to unknown pathogens or pathogens undetectable with current technology may occur.

Patients receiving care in all participating treatment centers will be asked to voluntarily provide a blood specimen annually of no more than 5-13 ml that will be tested for the presence of hepatitis B virus, human immunodeficiency virus (HIV). Blood samples will also be tested for other blood borne pathogens including but not limited to West Nile Virus (WNV), the dengue virus, and the parasite that causes Chagas Disease. The remainder of the blood specimens will be stored for future detection of viruses, diseases or conditions of particular importance to persons with sickle cell disease or thalassemia. All participants will receive pre- and post-test counseling at their treatment center regarding the implications of infection with hepatitis and/or HIV.

Specimens will be prepared according to guidelines provided by CDC and mailed using appropriate packaging to the CDC Serum Bank located in Lawrenceville, GA within 24 hours of collection. A lab form with the patient's CDC ID number will accompany the specimen. Clinicians will be responsible for sending the CDC any history of hepatitis B or HIV infection with the patient ID in an e-mail at the time of specimen shipment. The CDC Serum Bank will send specimens to the CDC Division of Blood Disorders Laboratory for hepatitis, HIV, and WNV testing. Any remaining blood will be stored at the CDC Serum Bank. Testing will be conducted at the CDC laboratory according to an algorithm provided by CDC that is based both on the results of previous testing and on current evaluation standards and practices. Information about vaccination status and the results of previous viral testing will be collected and used to determine the need for further confirmatory testing.

In the event of a positive laboratory finding, the CDC will contact the clinician for the participating site. Clinicians will proceed with the appropriate follow-up protocol at their institution based on these results. Clinicians will be responsible for informing patients about their laboratory results.

Data Collection

In addition to the risk of blood-borne infections, the CDC seeks to gather information about other complications of sickle cell disease and thalassemia treatment. Clinical and demographic data will be collected using direct patient interview by staff as a part of a routine clinical encounter. Information will be collected on a range of complications, including, but not limited to, the following:

- **Transfusion Regimen:** The amount and frequency of blood transfusions impacts where the patient stands on the continuum of anemia to iron overload. Information collection will include the indication for transfusion, degree of red cell antigen matching, and adverse transfusion reactions, including antibody formation.
- **Chelation Regimen:** Effective iron chelation can reduce iron-related complications; however, side effect of currently available therapies may further complicate thalassemia. Data collection will include dosing and frequency of chelation medications; and toxicities.
- **Procedures:** Surgical procedures such as splenectomy, cholecystectomy, and central venous access device placement are common in patients with chronic anemia and may result in significant complications.

Data entry will be done by the treatment centers through a paper-based form faxed immediately to the Michigan Department of Community Health (MDCH). The MDCH program coordinator will enter data into a password-protected database using Microsoft Access. CDC staff will perform reliability checks on the entered data and will periodically generate reports for use in clinical care and for use in monitoring prevention interventions. All data collection forms will be linked to biospecimens using the CDC ID.

Data generated by this surveillance system will be used to manage public health programs. The project is considered to be non-research by the CDC because it involves the regular, ongoing collection and analysis of



health-related data conducted to monitor the frequency of occurrence and distribution of disease or a health condition in the population. The primary intent of this project is to prevent or control disease or injury in a defined population by producing information about the population from whom the data were collected and no analytic (etiologic) analyses will be conducted. Hypothesis testing is not part of this project. For more information about public health research and surveillance, visit: <http://www.cdc.gov/od/science/integrity/docs/cdc-policy-distinguishing-public-health-research-nonresearch.pdf>

III. Risks

Blood will be drawn as part of other blood drawing procedures wherever possible. There may be some discomfort to patients associated with drawing blood. 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 during the visit. Some questions may cause embarrassment to very sensitive patients.

IV. Potential Benefits

The potential benefits to patients include the knowledge of whether or not they have been exposed to hepatitis B virus or human immunodeficiency viruses. Patients infected with a virus or other pathogen 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 or no symptoms. Early detection of viral infections can help physicians better plan the future care of their patients. Finding the source of the infection can also help prevent further spread to others. Patients who have a negative blood test for pathogens will benefit by being reassured that they are not infected.

V. Inclusion and Exclusion Criteria

All persons with a laboratory-confirmed diagnosis of sickle cell disease or thalassemia who have received at least one transfusion in the past year at the participating clinic site will be eligible for participation. This includes transfusion-dependent and intermittently-transfused patients with thalassemia and sickle cell disease (including all variants). There are no age restrictions and no limitations to participation based on gender, race or ethnic background. Approximately 800-1000 patients across the United States will be participating in this study, including approximately 100 study participants from Michigan.

VI. Study Timeline

All persons participating in the study will participate for two years by providing a biospecimen and responding to health-related study questions once per year. In the event that program funding continues beyond these initial two years, participants may be asked to continue participation.

VII. Informed Consent Process

The hematology staff will explain the nature and purpose of the project to the study participant. A brochure describing the program will be provided to all participants. Verbal consent must be given by all participants before enrolling the study. Clinical staff may obtain written informed consent for both donation of a blood specimen and collection of clinical data if desired by their institution. Parental permission for participation will be obtained for all minors.

The PI and staff at clinic facilities will explain in detail all aspects of the study to the prospective subject and/or legal guardian in order to minimize the possibility of coercion or undue influence. All four Michigan clinic sites have been providing care to these special population groups affected by these disorders for many years.



VIII. Other Protocol Elements to Consider

Payment and Reimbursement

Subjects will not be reimbursed for any activities related to this project.

Privacy Interest of Subjects

The subject's participation in this study will be noted in his or her medical record. If the subject's primary care physician is different from the study physician, the primary care physician will be notified.

Confidentiality

All participants will be issued a CDC ID number to protect their identity. Confidentiality of all records and materials will be guarded to the fullest extent possible. Signed consent forms and paper copies of the completed form will be kept in locked files at the participating clinic sites. No personal identifying information will be contained in the records maintained at CDC. In addition, these records will be stored 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. CDC or their designate will inspect the records relating to participant's involvement in the study. Data that does not directly identify the subject may be published in medical journals or shared with others as part of scientific discussions. No information from the subject medical records or study data will be held or processed except as it directly relates to surveillance for blood borne pathogens and complications of transfusions.

Data Management and Statistical Analysis

Analyses of the data collected will be used to guide programmatic activities of the CDC and MDCH. 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.

Analyses of patients at enrollment will yield prevalence rates of infection and other transfusion-related procedures and complications in the population. Test results obtained on the same patients in subsequent years will be used to calculate rates of seroconversion. These analyses will be descriptive in nature and will focus on highlighting demographic and geographic variability of rates.