BLOOD BORNE PATHOGENS SURVEILLANCE PROJECT

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Version: VI Date: January 12, 2002

Association of Hemophilia Clinic Directors of Canada (AHCDC)

1.0 Study Overview:

Since the middle of the last century, patients with bleeding disorders have been effectively treated with blood and blood products to stop their bleeding. These treatments have been life saving in many situations, and have led to a dramatic improvement in the length of life and quality of life of people with bleeding disorders. Unfortunately this treatment has been complicated by transmission of infectious diseases such as hepatitis and AIDS. Pooling of blood products from thousands of volunteers led to better products, but this also meant exposure to blood and the viruses it may contain from thousands of volunteers. The development of screening tests for the blood borne viruses and methods to remove these infectious agents from the blood products has fixed this problem, but patients, physicians and governments remain concerned about the possibility of new, unforeseen agents entering the blood supply and causing problems in the future. Gene therapy of hemophilia will likely avoid these problems, but may be complicated by other side effects.

The government of Canada, through the Blood Borne Pathogens Division, Population and Public Health Branch of Health Canada has asked that the Association of Hemophilia Clinic Directors of Canada (AHCDC) develop a method to look for known and emerging blood borne diseases. The project described here will establish a secure bank of samples to test for known blood borne infectious agents, and genetic changes causing or modifying the clotting disease and to be available for testing for newly discovered viruses and clotting gene changes as they are found.

2.0 Study Design

2.1 Consent

Patients are sent a letter, approximately one month before their Annual Comprehensive Hematology Clinic appointment to remind them of their appointment date and time. At this time, we will attach a brief note to the letter to inform them of the Blood Borne Pathogens Project.

We will also include the patient information sheet and the informed consent form. There will be clear instructions not to sign the informed consent sheet, until the participant is at the
Annual Comprehensive Hematology Clinic on the day of their annual visit, either with the nurse coordinator, or the physician investigator.

On the scheduled day of their Annual Comprehensive Hematology Clinic appointment, the research nurse will be present to obtain consent from the persons who wish to participate in this study. The patient may also be enrolled on any visit to the clinic or associated hospital.

The patient information sheet and consent form will be completely reviewed and then signed at this time.

The Physician Investigators and/or the Nurse Coordinator may obtain and receive telephone consent.

If the patient does not consent to participate in this study, at this time, we would like to ask them a few questions regarding their decision. They have the choice to either answer these questions or not. Please see attached Refusal Form.

### 2.1.1 Length of Study

In order to conduct serial testing of the blood samples for the purpose of this Surveillance Project, we would like to request re-consent every year for all participants, until such time as:

1. Patient no longer wants to participate in this project.
2. The project ends.
3. Patient expires.

### 2.1.2 Re-consent

i. We would like to ask all participants, if they are willing to re-consent to continued yearly participation in this surveillance project.

ii. If they re-consent, their participation would require additional blood samples every year during their annual visit.

iii. If they agree, they will be contacted by phone or mail when the designated time has expired, (no less than 8 months after the blood samples have been given) and an appointment will be booked for the participants to visit the clinic and give the blood samples.

iv. When the participant arrives at the clinic, the nurse coordinator will review the study and have them re-consent by way of signing the *Re-Consent form.* (See attached form)

v. If the participant, changes his/her mind at this time and refuses continued participation, then the nurse/or physician will document this and ask if the study may keep the previous samples of blood and any clinical information collected and proceed as they had initially consented for, one year prior.

vi. If the person refuses to allow continued use of their samples, this will be documented. Then the samples and any clinical information collected will be destroyed. This will be documented on the Destruction of Samples Form.

All documentation will be maintained with the patient’s case report forms.
2.2 Sample Collection

Blood collected from people with bleeding disorders will be labelled with a registry number and sent to a central surveillance lab, currently in Edmonton. No other identifying information will be on the tubes, so that the sample bank will know no information that can identify the patient. In the lab, the blood will be processed to collect plasma (the liquid that the cells float in), DNA and RNA (the genetic material of the cells). These samples will be given a new number known as an inventory number, which will be used for further testing, (so that no information that can link the sample to a patient) when samples are made available to any testing facility.

2.3 Data Collection

Clinical data collected through the current database, CHARMS, and labelled only with the CHR (Canadian Hemophilia Registry) number, will be further encoded with a new appointed barcode inventory numerical identifier, and transferred to a central server.

2.4 Sample Testing

Samples will be tested only in labs specifically contracted to the AHCDC. Contracts will include the statement that:

- No other testing than that described herein, will be done, and that test results will be reported to the AHCDC in a timely fashion. Samples will be labelled only with an inventory number, so that no identifying information is available to the testing facility.

Notice will be given to all associated REB of:

i. Each new test. (This includes only tests covered by the consent provided here. Any test not covered in the consent must have a separate consent.)

ii. Receipt of all results after the tests has concluded (not the results themselves.).

2.4.1 Sample Storage

All blood samples will be stored at the Central Surveillance Laboratory located at the:

University of Alberta
471 Medical Sciences Building,
Edmonton, Alberta, T6G 2H7

under the direct supervision, and care of, of Dr. Bruce Ritchie. The samples will be stored and used for 20 years, and at that time, if possible, apply for a extension for the sole purpose of extending the testing requested, and required for this study.

2.5 Handling of Results

Test results will be sent in a timely fashion to the research subcommittee of the AHCDC, to an oversight board, and to the clinics that sent in the blood samples. The AHCDC committee and the oversight committee will only be given summarized data, while the clinics will be given test results linked to the registry number (CHR) of the patient, so that the patient can be notified of their result.
The Blood Borne Pathogens Division, Population and Public Health Branch of Health Canada, has agreed to provide guidance for counselling patients who have been found to have evidence of exposure to a new blood borne pathogen.

As the trial progresses, summary results may be reviewed and analyzed by other international committees, as designated by the Research Subcommittee of the AHCDC. The data will be shared with international online databases of specific mutations.

3.0 Administrative Structure

3.1 The Research Subcommittee of the AHCDC

The Research Subcommittee of the AHCDC is made up of AHCDC members. They are responsible for overseeing research done on behalf of the AHCDC.

3.2 The Surveillance Oversight Committee

The Surveillance Oversight Committee is made up of members of the Canadian Hemophilia Society (CHS), the AHCDC, the Blood Borne Pathogens Division, Population and Public Health Branch of Canada, the Canadian Blood Service (CBS), and an ethicist, currently Dr. John Dossetor, who was awarded the order of Canada for his work on medical ethics. They will provide oversight and general recommendations about the handling of studies and results.

4.0 Scientific Rationale

4.1 Canadian Hemophilia Registry

The Canadian Hemophilia Registry (CHR) was formed in 1988 by Dr. Irwin Walker from Hamilton, Ontario as a project of the Canadian Hemophilia Clinic Directors Group (CHCDG), the forerunner of the Association of Hemophilia Directors of Canada (AHCDC).

Initially, the CHR was formed to count and describe the Canadian hemophilia population. It also allows provides the clinics with a tool to follow patients receiving coagulation blood products. The CHR consists of a minimum data set of anonymous data, suitable for a variety of research and administrative purposes. This is the only source of validated national data available and is a key tool for the national blood product inventory and tracking system, known as CHARMS. Anonymous summary data from the CHR has been supplied, on request, to federal and government agencies, the Krever Commission of Enquiry, the Canadian Hemophilia Society, pharmaceutical companies, and individuals most of whom are students and research fellows.

The CHR consists of a minimum data set on each client, currently kept in an MS Access database. Items included are as follows: clinic name, patient identification code, date of birth, factor deficiency type, severity of the deficiency according to factor levels (severe <1%, moderate 1-5%, mild >5%), the HIV antibody status, and the hepatitis status. The CHR computer assigns to each subject an exclusive number, termed the CHR number. This minimum data set is maintained and reviewed continuously. Additional data sets for specific projects are added, but not maintained once projects are completed. Noting combinations of recurring birth dates and extra identifiers identifies duplicate entries due to individuals
registering with more than one clinic. Confidentiality and security measures include the use of anonymous data, restricting database access, password protection, the use of a secure operating system such as Windows 2000, and placing the computer in a restricted area. Security of identifying demographic data remains in the individual comprehensive hemophilia clinics.

Updating and validation of the registry has occurred about every twelve months in response to requests from the director. The clinic directors are sent lists of CHR data pertaining to their clinics with a request to check for errors, transfers, new entries, deaths and duplicate registrations. Data managers will formally take on the updating of data, and updating/validation will be done on an ongoing basis.

4.2 CHARMS

Since 1995, the AHCDC has developed and implemented a national electronic medical information database, called CHARMS (the Canadian Hemophilia Assessment and Resource Management information System), to track use of clotting factor concentrates. CHARMS has been supported by the Canadian Blood Agency previously, and now the Canadian Blood Services and Hema Quebec. The goal of this project is to track coagulation product use so as to provide accountability of product use, and data useful to plan future purchases.

CHARMS also functions as an electronic chart and has been designed to collect the usual clinical data that is kept on the patient chart, including information such as infection status (hepatitis, HIV), vaccination status, CD4 count, liver function tests, complete blood counts and orthopaedic staging following joint bleeding. Unlike product utilization data, the clinical data is collected at the discretion of the individual clinics, and is kept within the clinics themselves. Central, coded collection of this data for correlation with the outcome of blood-borne infectious disease and for correlation with molecular genetic characterization is key to the success of this proposal.

4.3 Potential Transmission of blood-borne Disease in Blood Clotting Products

4.3.1 Transfusion Transmitted Viruses

Since the mid 1970s, treatment of bleeding disorders by replacement of coagulation factors with blood products has involved the use of pooled blood products. These pooled products are made from pools of thousands of donors, and in the past, they have transmitted hepatitis A, B, C, and G, human parvovirus, and HIV, the virus that causes AIDS. Now coagulation blood products are tested to remove any donors who have been exposed to known blood-borne infectious diseases and then the blood products are treated with techniques to inactivate any remaining undetected viruses. Effective methods of viral inactivation include the steps involved in the clotting factor purification process as well as pasteurization, solvent/detergent treatment, and nanofiltration. A combination of methods, usually three, is commonly used, since no method alone is effective against all blood-borne infectious agents. Since the introduction of modern effective methods of viral inactivation, used in combination, no cases of transmission of disease by these products have been discovered.

Despite the clear success of viral screening of donated blood and viral inactivation of pooled blood products, new infectious or viral agents continue to appear which may or may not cause disease upon transmission through blood products. In 1999, Danielle Primi, working
with the biotechnology company Diasora in Italy, reported the SEN-V virus. A pilot study has been undertaken by Health Canada AHCDC to determine the significance of this in the Canadian hemophilia population.

4.3.2 Prion Diseases

The prion agent that causes a disease known as scrapie in sheep can be transmitted in feed to cattle causing bovine spongiform encephalopathy (BSE) also known as Mad Cow disease. This in turn can be transmitted to humans who eat beef, causing variant Creutzfeld Jacob disease (variant CJD). Because of this concern Hema Quebec and the Canadian Blood Service have banned donors who have resided in the UK. In 1998, Health Canada placed a temporary “hold” on Recombinant FVIII, which was produced in tissue culture containing plasma protein from a man who later came down with CJD. The recombinant FVIII was cleared for use after studies showed that the donor in question had had classical CJD and not the variant form. Although there is concern about transmission of variant CJD, current evidence indicates that classical CJD is not transmitted by blood. In addition, Bayer Corp. has published the results of internal testing showing that prion agents are effectively cleared by their purification methods. Recently, assays for the agent causing CJD in biological fluids have been described.

4.3.3 Endogenous Retroviruses

The normal DNA in all the cells of humans and other animals contains genetic sequences, which code for retroviruses, similar to HIV. These genetic sequences are known as endogenous retroviruses. They likely represent infection in distant ancestors, which integrated into the DNA of the infected animal and have been passed by inheritance and evolution from parent to offspring since. They then evolved separately in different animal species. These genetic sequences apparently do not cause disease, but concern has been raised, about the transmission of endogenous retroviral elements between species through transplantation of tissue. Pig cells in tissue culture can release porcine endogenous retrovirus (PERV) under appropriate conditions and these are able to infect human cell lines in tissue culture. Work by the Food and Drug Administration (FDA) in the US has found no evidence of transmission of PERV to humans, although there remain concerns by investigators and regulators. Use of porcine FVIII in patients with inhibitors is of concern in this context, although there has been no reported evidence of such transmission. The development of new tools, such as western blotting, will aid in screening for transmissible endogenous retroviral elements.

4.4 Molecular Genetic characterization of clotting disorders.

Modern molecular genetic techniques have revealed a wealth of information about the genetic defects leading to bleeding disorders. For over a decade now, members of the AHCDC have contributed detailed anonymous information to international databases of genetic mutations, which make detailed genetic, functional and structural knowledge widely available. Matching of a genetic mutation with a change in the function and structure of clotting factors and biological change in the person affected provides a wealth of detail about the function and interaction of blood clotting factors. For instance, discovery of the interaction of the coagulation protein Factor V with the anticoagulant protein known as protein C, suggested that mutations in the Factor V gene (Factor V Leiden) which cause a mild hypercoagulable state, might modify the severity of bleeding in severe Hemophilia A. Members of the
AHCDC have collaborated to confirm this moderating interaction of Factor V Leiden on severe Hemophilia A.

Continued technical advances have greatly sped up the characterization of mutations causing disease. High speed DNA sequencing using robotic work stations, fluorescent nucleotides, and high speed capillary electrophoresis has allowed characterization of the entire human genome by both a commercial group (Celera Genetics) and an international consortium (HUMAN Genome Organization, HUGO), years earlier than expected. Silicon chip based sequencing has simplified the characterization of known genes and silicon chip based hybridization can determine the level of activity of any known gene in different tissues. It is now possible to correlate clinical/biological characteristics of individuals with bleeding disorders, with their genetic make-up. The collection of clinical data, DNA and RNA are key first steps in such work and are at the heart of this proposal.

Current gene therapy protocols for the most part involve viral vectors. Because of concerns about the interaction of these viral vectors with the genomes of their human hosts, these protocols require that DNA be banked prior to beginning treatment. A collection of DNA from all patients with congenital bleeding disorders will greatly facilitate this work.

It may be possible to correct point mutations in living animals using a technique known as chimeroplasty. Given recent problems with gene therapy using viral vectors, chimeroplasty may become the preferred method of gene therapy for bleeding disorders. Knowledge of the specific mutation in each patient will be critical prior to attempts to correct these mutations.

Genotyping is also important for the progression of infectious diseases such as hepatitis C and HIV, which complicate hemophilia. In these situations, the genotype of the virus and its host can help predict the outcome of the disease.

We primarily propose to collect blood for banking of plasma, DNA and RNA for use in screening known and emerging blood borne infectious diseases. Our secondary purpose, is to collect blood for banking of DNA, and RNA to identify the genetic mutations causing bleeding disorders and to characterize interacting blood clotting genes.

5.0 Study Objectives

5.1 Objective

The objectives of this project are:

1. To collect blood samples for a sample bank of plasma, DNA, and RNA to screen for known and emerging blood borne diseases.

2. To identify the mutation leading to each consenting patient’s bleeding disorder, and to characterize other known and yet to be discovered genes that affect blood coagulation.

3. To collect encoded, non-nominal data into a central database from an electronic chart known as CHARMS, which is currently kept in each hemophilia clinic in Canada to correlate with results from 1 and 2.
6.0 Study Population

6.1 Patient Inclusion Criteria

To participate in this surveillance project, the patient must have:

? A diagnosed hereditary bleeding disorder.
? Be between the ages of 0 – 85.
? Consent to be informed of all future testing results as they are discovered through this surveillance project.

A person must be willing to be informed of all the results which may be available as testing is done. Participation is not accepted if the participant refuses this. This is not an option. Therefore consent reads:

☞ I am aware that the results of all-future testing will be given to me.

6.2 Patient Exclusion Criteria:

The following is the list of the exclusion criteria:

? Persons who are unable to consent due to mental inability will not be able to participate in this study.
? Person who is known/diagnosed alcoholic may not participate in this study.
? Person that the investigator, and/or the co-investigator deems as unfit for this trial may not be enrolled in this study.
? Patients, who refuse to consent or participate, will not be enrolled in this study.
? Patients, who do not consent to be completely informed of all testing results as they are discovered, will not be eligible for this study.

6.3 Sample Size

The sample size will be based on the total number of hemophiliac patients documented here in Canada with the help of the Blood Borne Pathogens Division, Population and Public Health Branch of Health Canada. We expect to enrol 3,500 patients throughout Canada.

7.0 Study Design and Procedures

7.1 Study Summary/Flow Chart

The study begins at home with the brief letter to introduce the study, and the REB approved Patient Information sheet and Informed consent form.

Patients have specific instructions not to sign the Informed Consent Form until they are in the presence of the Physician Investigator and/or the Haemophilia Nurse Coordinator.

If the patient consents to participate in the surveillance study, the required blood samples will be taken along with their routine blood tests. This will avoid having the patients accessed twice for blood samples.
If the patient does not consent, there will be no blood samples taken.

After the lab assessment, the patients are then sent to the designated clinic office to continue with the rest of their appointments, for their Annual Comprehensive Haematology Clinic. This means, assessment by an orthopaedic surgeon, physiotherapist, dentist, social worker, and nurse co-ordinator are usually performed. The patient will receive their routine check-up, along with a complete physical exam and routine vital signs. Please note these procedures may vary with each Hemophilia Clinic.

7.2 Procedure Description

The study personnel will explain the procedure to the patient. Please refer to the Patient Information Sheet.

7.3 Informed Consent

Informed consent can be obtained at this time, only if the patient information sheet has been reviewed, and all questions have been appropriately and completely answered. If the person understands the study and agrees to participate, the patient now signs the informed consent form. The original should remain on the chart and a copy given to the patient.

7.4 Evaluation of Inclusion/Exclusion Criteria

After the participant agrees and signs the consent form, the study nurse will review the inclusion and exclusion criteria to ensure that the participant understands and accepts the responsibility of being informed of all the information that may be discovered with this project. If the patient meets all criteria, they will proceed with their participation in the study. If the patient does not meet all criteria, they will not be allowed to continue their participation in the study.

We will also record the information regarding the reasons of non-participation in this study. We would like to ask why the person did not consent. Was it due to the project’s objectives, being informed of all results, or other reasons? This information may help us analyze the needs and requirements of participants in the future.

All the information will be recorded on the Enrolment Data sheets.

7.5 Laboratory Evaluation

In addition to the routine blood sample, qualified, and certified personnel will take an additional sample of blood.

For infants and children between the ages of 0 - 4 years of age, only 2.5 cc of blood will be taken, an equivalent of 1/2 teaspoon.

For all other participants age five or greater, 5-12.5 cc of blood will be taken, an equivalent of 1.0-2.5 teaspoons. The sample will be obtained at this visit, and will be labelled and shipped (Per Protocol/ Lab Manual/ Standard of Practice) to the study centre:
7.6 Data Management

Currently, clinical and laboratory data is entered into the MS Access database known as CHARMS at each individual clinic. Non-identifying data from patients who consent will be transmitted to a central database using the software known as Internet Clinic Trial Manager. Data is first encoded with the Canadian Hemophilia Registry (CHR) number, and then data entered in the central database is given an individual database identification number, which is used for all future work. All data is stored using state of the art encryption, and data transmissions will be done by using a secure method such as Secure Socket Layer (SSL) transmission or Secure Shell (SSH).

8.0 Study Completion/Withdrawal

8.1 Study Completion

There is no further requirement from the participant at this time.

8.2 Disposition of Blood Samples

Once a blood sample is obtained, it will be labelled with the CHR number and barcode, and shipped to the coordinating study site located at:

University of Alberta Hospital
471 Medical Sciences Building
Edmonton, Alberta. T6G 2H7

Under the direct supervision of Dr. Bruce Ritchie, the primary investigator identified in this project, the blood samples will be processed, maintained and stored. Samples will be given an inventory number for storage, and the code linking the CHR number and inventory number will not be released from the surveillance lab. (Please refer to the Laboratory Manual for guidelines of blood draws, certification documents of lab and personnel, and standards of practice.) Blood will be processed to purify DNA, RNA, and serum, which will be split into aliquots and stored.

The blood samples that are taken for the purpose of this study will be stored at the coordinating study site; The University of Alberta Hospital, Medical Sciences Building 471, in Edmonton Alberta. These samples will be stored for the length of the study, so that they can be tested for emerging infectious agents, and emerging coagulation genes as they are identified. Due to the numerous number of tests that may be applied to the samples.
8.3 Storage Failure:

All the samples will be stored in the freezer, documented on the Clinical Lab Manual. In the case of electricity failure, this freezer has a continuous CO2 back up system, which immediately starts when the temperature increases from the set determined degree of -80°C. There is also a subsequent alarm system which is linked with the security office, (University of Alberta Systems Monitoring) which enables them to immediately contact Dr. B. Ritchie, and/or Dr. J. Hooton, of this occurrence, so that measures can be taken to fix the problem and maintain the standard required for the storage of all the samples.

8.4 Testing of Samples

Samples may be shared with other researchers working on emerging blood borne infectious agents or genetic changes affecting blood clotting only. Such work will be done under contract, which includes a statement that no other un-consented testing will be done and that the results will be reported back to the AHCDC research subcommittee in a timely fashion. No other work or study may be conducted on these banked samples other than what is specifically outlined in this protocol, and covered in the contract between the AHCDC and the testing facility. Studies of new or emerging blood borne infectious diseases or genetic defects, which are covered by the consent, but have not been previously described will be presented to the research committee of the AHCDC for approval. Individual REB’s will then be notified that such testing will be carried out.

Any other/new studies, not covered by current consent, will be considered by the research committee, but will not be carried out until appropriate consent is obtained. This must be presented as a peer reviewed protocol and approved informed consent form.

The genetic material and serum samples will not, in any way, be sold or used for any commercial purpose. No other work, other than what is outlined in this protocol can be done with the samples. Any additional research, not covered by this consent, must have a new informed consent and protocol.

The samples will be identified at the study centre only by the CHR number, which has been predetermined (AHCDC), and labelled by the participating site. Samples sent to a testing facility will be labelled with an inventory number only. The code linking the CHR and inventory number will be kept at the surveillance lab, and will not be shared outside the facility. The link of the CHR number to the participant's name and other information will remain at the individual clinic site and will not be revealed to the surveillance lab or study centre. Thus, the identity of each participant will remain anonymous.

Each participant will be informed of all the results of consented genetic testing. Test results will be communicated to the clinic with the appropriate CHR number, which will allow the clinics to identify the patient concerned. Participants will be notified of the results of such testing by the clinic physician at the first opportunity. The Blood Borne Pathogens Division of Health Canada will provide assistance in counselling patients about these findings.

It is the sole responsibility of each site-specific co-investigator to be the person, responsible for informing each participant of the results of the genetic testing. However, it is the participants' sole responsibility to inform the site-specific co-investigator of any name change, move, change in contact number, etc. The site-specific co-investigator is then
responsible for the maintenance and storage of all records for each participant for the purpose of this project.

All of the above information is specifically outlined in the patient information sheet and a copy will be given, and copies made readily available if the participant loses the original.

8.5 Study Withdrawal

The patient is able to, at any time, to withdraw from the study. The patient is only required to contact his/her physician and inform them of their choice to withdraw. It is then, the site-specific co-investigators responsibility to contact the coordinating study centre and inform them of the patient's choice to withdraw. This will then enable the study centre to discard the blood sample, which prevents any further testing from that point.

8.5.1 Destroying of samples:

If a patient refuses continued participation, at anytime after enrolment in to the study, they will need to inform the appropriate clinic investigator, who will then be responsible for informing the Central Lab.

As soon as verified notification is received, in the form of a signed and dated document, the central lab will take the remaining samples and destroy all of the remaining samples, when an independent observer is available to witness the destruction. This will be done according to the lab manual, under Standard of Practice.

8.5.2 If a patient expires

If a patient expires, due to any circumstances, they have the decision at the time of enrolment to dictate what should happen to their samples.

The choices are:

1) All of their samples to be immediately destroyed upon receipt of the first notification of their death at the Central Lab.

2) Samples may remain in the study and can only be used in direct accordance of the specific protocol for which it is intended.

Ownership will remain in the responsibility of the governing committee directly involved with the study.

Therefore this will be included on the Informed Consents:

✔️ I wish to have my samples destroyed upon my death.

✔️ I wish to have my samples remain in the study, for further study, as outlined in my signed consent.
8.5.3 Consent for continued participation after death:

At the time of death, where continued participation is consented by the deceased, notification to the family, significant other, and/or legal guardian will occur.

9.0 Statistical Consideration

Statistical Evaluation will depend on the particular testing being done, which will determine the sample size, and statistical significance. Further statistical analysis will have to await decisions about specific testing.

10.0 Responsibilities of the Investigator

10.1 Introduction

This study will follow Good Clinical Practice guidelines, as established by Health Canada and the Food and Drug Administration (FDA).

Health Canada acknowledges the GCP of the International Conference on Harmonization (ICH) but all research through Canadian Universities is also covered by the Canadian Tri-Council Policy Statement for Research involving Human Subjects (TCPS-1998).

The Therapeutics Products Program (TPP) of Health Canada is the national authority that regulates drugs, medical devices and other therapeutic products used in Canada. Clinical trials conducted in Canada are subject to Good Clinical Practice, the Declaration of Helsinki, and guidance regarding the conduct of clinical trials issued by TPP.

The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific and regulatory communities. They are not to impede or restrict research.

The ethical standards defined with the GCP are intended to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not.
- The study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the finding;
- The potential benefits of the research justify the risks.

In this surveillance project, Health Canada has read and approved the grant, which is the sole financial supporter for the creation and implementation of this project. It is the primary investigator Dr. Bruce Ritchie responsibility for the following:

- To select qualified co-investigators
- Provide each co-investigator with the information that they need to properly conduct the study at their site/clinic.
- To assist each co-investigator with all/any aspects of this study, and to ensure that the trial is conducted professionally and ethically, abiding to all regulations and guidelines that have been developed for clinical trials.
- Ensuring proper monitoring of the investigators
Ensuring that the study is conducted according to the BBP Protocol.

The primary investigator and the co-investigators are solely responsible for protecting the rights, safety, and welfare of all subjects entered into this project, and all information that may be obtained or discovered. All participants have the right to know, and must be informed of all information obtained and discovered as a result of their consent to use their blood for this project.

11.0 Legal and regulatory Consideration

11.1 Compliance with Law, Audit, and Disbarment

Each investigator, with current GCP standards and in conformity with the Canadian TCPS (1998) guidelines, is responsible to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal and local laws, rules, and regulations related to the conduct of a clinical study.

Each investigator is required to make all study documentation properly available for inspection, review, or audit at each study site upon request by any appropriate regulatory agencies, the principal investigator, and its' representatives.

Any individuals ineligible from conducting or working on clinical studies, including those who are ineligible as a result of disbarment, will not be allowed to conduct or work on this project. The person is required to disclose immediately, in writing to the primary investigator if any of the above is, or may be applicable, as in the case of a pending, or threatened legal action.

12.0 Protection of Human Rights

12.1 Subject Consent

Each participating site will be provided with a sample patient information sheet and consent form. Although the use of these developed documents is recommended, these forms may be adapted to suit the needs of each institutional review board with the acknowledgement, acceptance, and approval of the primary investigator and the appointed study centre coordinators.

The patient information sheet must include the following:

- Purpose of the study, and the design
- Participation involvement
- Risks and benefits
- Withdrawal from the study at any time without prejudice to further treatment at any time
- Confidentiality/Maintenance of records

13.0 Research Ethics Boards (REB)

Each co-investigator, with the continued support from the study centre, is responsible for obtaining approval of this project from their Research Ethics Board. The REB must also review any amendments, and approval must be in a form of written documentation. This approval document must be kept at each site, and a copy forwarded to the study centre.
The study protocol and the appropriate final version of the patient information sheet and the consent form must have written approval from the REB before any patient enrolment into the study.

14.0 Protection of Subject Data

The co-investigator, at each specified site is responsible for keeping and maintaining a record of all subjects participating in this project and link it to a CHR number which has already been predetermined as a patient with a bleeding disorder (blood disorder, hemophilia). However, no other persons will be able to link the designated patient number (CHR) to the individual. This is the only identifier, which will be used to link the blood samples taken and shipped to the study centre.

A confidentiality clause will be included in the patient information sheet to inform the patient that only authorized personnel, directly involved with this study, or regulatory authorities may have access to the records if deemed necessary, or for audits. All and any publications will never name a person, or provide any information by which any participant can be identified.

15.0 Modification of the Protocol

In the case that an amendment is made to the protocol, each site-specific co-investigator will be notified in writing, along with the amended protocol. All amendments must be reviewed by each site specified REB and have written approval of such.

The research subcommittee of the AHCDC, in consultation with the Surveillance Oversight Committee, will decide on whether or not significant changes in the protocol have been made. It is the responsibility of the Surveillance Oversight Committee to decide whether or not significant changes in the protocol have been made. If significant changes have been made, then consent for the changes must be obtained prior to doing the changed procedures. All necessary changes must be noted on associated documents. Ie: consent forms.

16.0 Study Records

16.1 Documentation

All documentation is the responsibility of each site investigator. The responsibilities are listed below:

1) Current and complete curriculum vitae for each site investigator. Signed and dated.
2) REB membership list (kept on file).
3) Approval of the protocol, patient information sheet and consent form from the REB. The study centre must be in approval of the patient information sheet and consent form if any changes were required, other than the original sent to the site.
4) Certification of the laboratory that is used for the purpose of conducting this trial.
5) Retain all approvals and correspondence with the IRB, and/ or study centre. All completed original informed consent forms with the required signatures. All shipment forms associated with this study
16.2 Subject Identification

Each site must keep an enrolment log, for each patient that is screened for the study. (Patient name, age, date of visit, and whether or not the patient agrees/or not to participate in the trial. This form will be standardised to capture the same information at all participating clinics. See attached enrolment log).

16.3 Recording of Data

The study centre will provide each site with a document for recording data, The Case Report Forms (CRF). This will help assist each site to a standard for data collection. (See appendix 3.)

16.4 Record Retention

Each site is responsible for retaining the documents for a period no less than 15 years from the completion of the study. If the documents need to be relocated, the site must notify the study centre. Each site is responsible for providing the information to the study centre as to where the documents will be stored, and who may have access to them in case the need to re-access information in the future were to occur. The location must meet certain requirements; a locked, secured room, with a functional and working water sprinkler.

16.5 Laboratory Certification

Each site must provide laboratory certification, which states that the lab chosen to participate in this study is accredited and all associated laboratory personnel to be certified as well, per guidelines and regulations. This document is to be kept on file.

16.6 Confidential Information

All information related to this project is completely and entirely confidential. All confidential data remains the sole property of the AHCDC. No information may be disclosed to others without the written permission from the study centre. At the discretion of the study centre, information from this study may be made available to Health Canada, other regulatory agencies (the FDA) and/or other physicians who are conducting similar studies.

16.7 Publication

The primary investigator, Dr. Bruce Ritchie, has the right to publish, independently, the results of this project. Authorship determination will be at the discretion of the research subcommittee of the AHCDC, and the principle investigator Dr. Bruce Ritchie.

Site-specific co-investigators are requested not to publish any results of this study without the written permission of the research subcommittee of the AHCDC. Such permission will not be unreasonably withheld. A copy of any manuscript based on this data must be submitted to the research subcommittee of the AHCDC at least 90 days before publication. The subcommittee will be allowed to comment on the manuscript and make comments and changes, as they deem necessary for the validity of the project. However, additional publication can only be submitted once the primary study analysis has been accepted for publication.