

Association of Hemophilia Clinic Directors of Canada

**Blood Borne Pathogens
Surveillance Project
Progress Report 2004-5
March 23, 2005**

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Blood Borne Pathogens Surveillance Project

1.0 Progress, 2004-5

- a. Audit March 17, 2005: On March 17, 2005 an review of the program was organized with Dr. Anthony Giulivi of ; and Dr. Mike Soucie and Sally Crudder of the Hemophilia Surveillance Branch of the Centers for Disease Control (USA). Dr. Giulivi was unable to attend at the last minute because of a personal crisis, however, Dr. Soucie and Sally Crudder did review the program. They reported verbally that they were satisfied with sample collection, sample processing, sample security, Standard Operating Procedure (SOP) development, and the BBPSP database. This group reviewed the recommendations of the 2004 audit group and agreed that security would improve through installation of an electronic door lock, and surveillance cameras. We are seeking funding for these items from external sources. They also agreed that tighter linkage between the CHARMS database and other research of the AHCDC would lead to a stronger outcomes surveillance program, although this is outside the scope of the BBPSP.
- b. Data for Health Canada:
 - a. Adverse Events Reporting from CHARMS – currently being released in CHARMS 3.1.0.
 - b. Blood Borne Infectious Diseases data from CHARMS – in place.
 - c. BBP data from approved research projects - as projects develop.
- c. Sample collection:
 - a. Clinic enrolment – all the major clinics in Canada are enrolling patients or are near to enrolling patients (Figure 1).
 - b. Plasma, DNA, RNA, cells archive growing exponentially – continuing (Figure 2). Current accumulated visits 771.
 - c. Sample management/testing Standard Operating Protocols - in place
 - d. Regular financial reporting, per attached schedule (Appendix C) – this is the first report following the first payment of funds for 2004-5.
- d. BBPSP website with key documentation:
 - a. Current status of clinic enrollment – in place
 - b. Current status of samples accrual – in place
 - c. REB submission information – in place
 - d. BBPSP Manual – in place
 - e. Results of testing – no testing yet done; we are in discussion with Health Canada labs in Winnipeg and Samuel Stanley of Washington University, St. Louis, Missouri, and the Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases.

- e. Maintain standards for sample shipping and handling, including:
 - a. ISBER membership - the BBPSP will join ISBER, the International Society for Biological and Environmental Repositories (<http://www.isber.org/>)
 - b. BBPSP staff are trained to provide TDG (Transport of Dangerous Goods) training and information for the participating labs.

- f. Re-negotiation of University of Alberta contract: The contract with the University of Alberta has been re-negotiated and now clearly places control/ownership of samples in the hands of the AHCDC, and clarifies indemnification, insurance requirements etc.

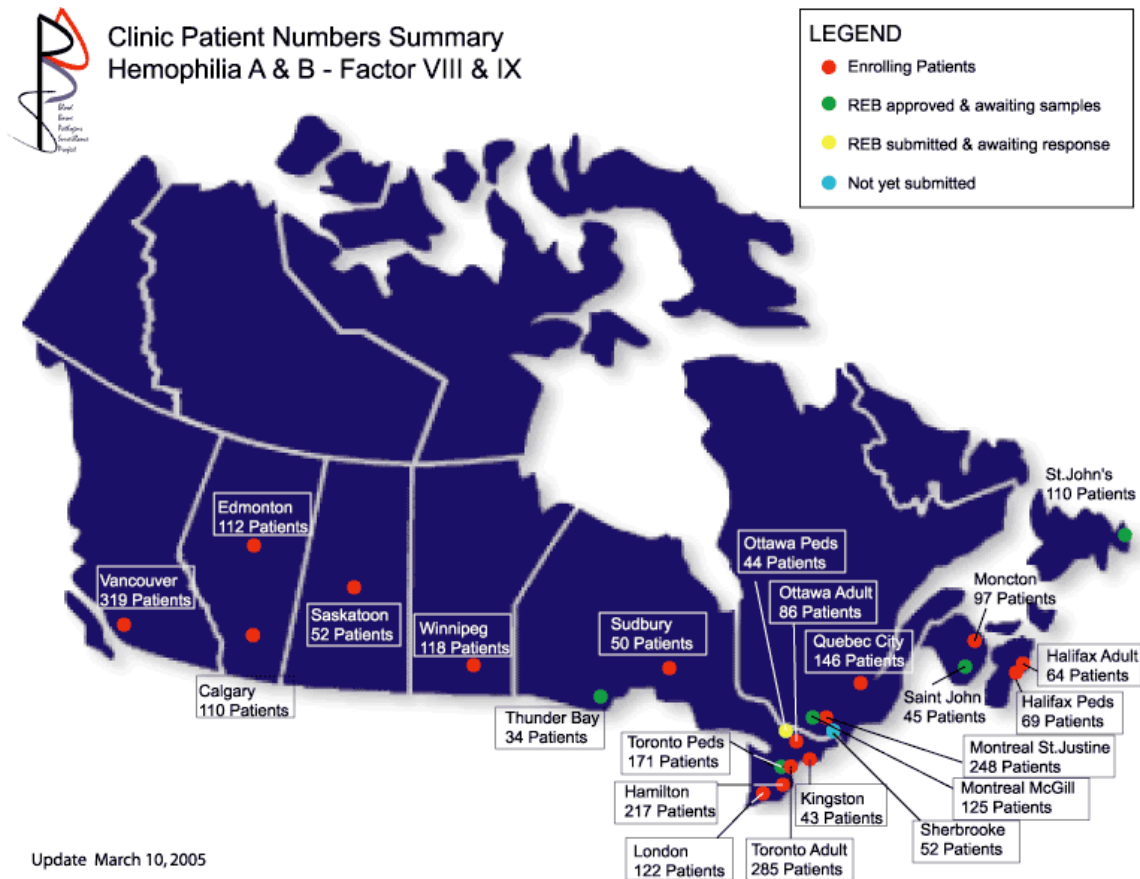
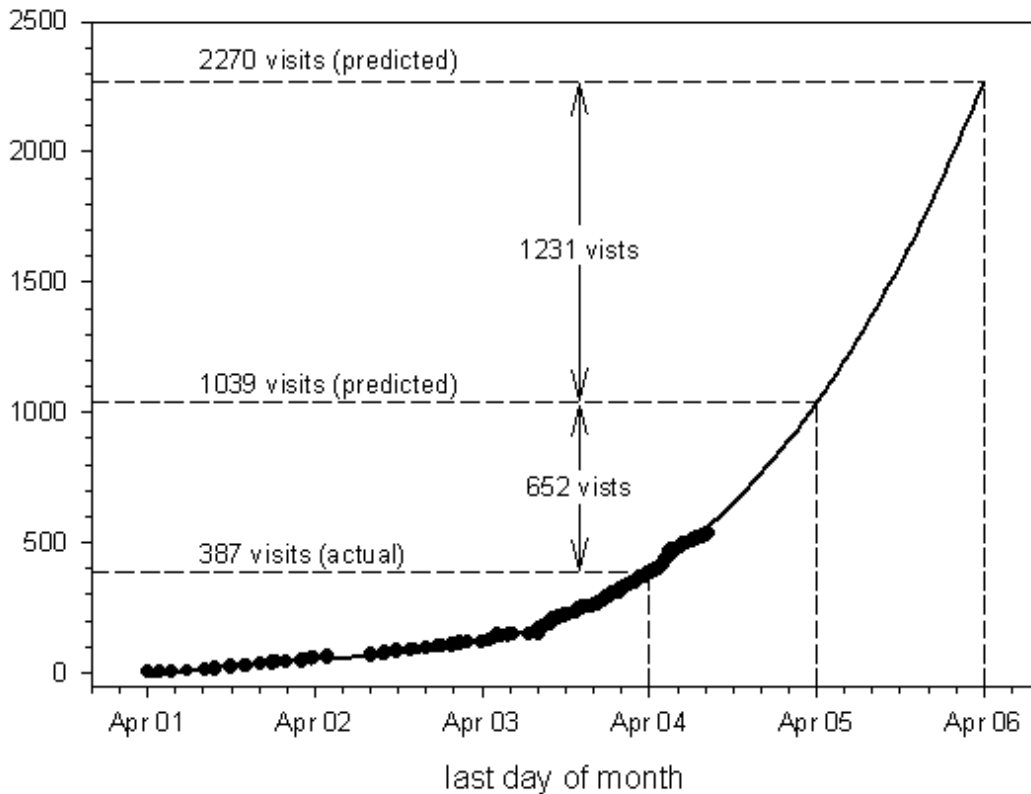


Figure 1. Clinic status.

BBPSP Number of visits as function of time



$$\begin{aligned} \text{fitted curve: } y &= y_0 + ax + bx^2 + cx^3 \\ y_0 &= -15.736 \\ a &= 10.893 \\ b &= -0.660 \\ c &= 0.019 \end{aligned}$$

Figure 2. Sample accrual, measured as patient visits, as a function of time.

2.0 Background

The problem:

Blood Borne Pathogens are an ongoing problem in Canada. Modern screening of blood and plasma donors with clinical examination, blood quarantine, serologic testing, and nucleic acid testing, in addition to improving methods of viral inactivation have dramatically improved the safety of the blood supply, but new pathogens continue to emerge as fast as the technology changes to deal with them. Recently two cases of “New Variant CJD” have occurred in people receiving blood products from infected blood donors. People receiving products made from pooled blood have been particularly at risk. The infection of large numbers of hemophilia patients with HIV and hepatitis C, and the slow response of the blood system were reviewed by Justice Horace Krever

in his report. A key recommendation of that report was for the development of a surveillance system for recipients of blood and blood products.

This project fulfills the surveillance recommendations of Justice Krever. It takes advantage of a number of advances in medical management over the last few years, including:

- A collaborative network, the Association of Hemophilia Clinic Directors of Canada (AHCDC), a network of clinics devoted to the management of rare blood disorders that require replacement with blood derivatives;
- A mature informatics systems consisting of a database for this archive as well as the Canadian Hemophilia Registry (CHR) and Canadian Hemophilia Assessment and Resource Management information System (CHARMS), modern registries and database systems that can correlate clinical outcomes with blood sample testing;
- Secure and robust archiving technology for archiving tissue/blood samples;

3.0 Project Overview

The network - AHCDC:

Canadian Hemophilia Clinic Directors have been collaborating in the investigation and establishment of national standards of care of patients with bleeding disorders for over 20 years. In 1993, the group was incorporated in the Province of Ontario as the Association of Hemophilia Clinic Directors of Canada (AHCDC). The same year, a report from the group led to the introduction and rapid adoption of recombinant Factor VIII in Canada, so that within a year essentially the entire Hemophilia A population switched to recombinant FVIII. At the request of the Canadian Blood Agency (CBA), AHCDC developed a coagulation concentrate tracking system (see CHARMS below), that has been implemented in all clinics in the country, and which links the clinics in a blood product tracking network.

The AHCDC has a strong track record of collaborative research, including the development of a central inhibitor lab in Kingston, the development of a mutation analysis lab, also in Kingston, the development of the Canadian Hemophilia Registry (CHR) and Canadian Hemophilia Assessment and Resource Management information System (CHARMS), and the collaborative development of national programs on prophylactic treatment, treatment of inhibitors, treatment of hepatitis C, and inhibitor surveillance. Collaborative research publications are summarized on the AHCDC webpage at <http://www.ahcdc.ca/>

The AHCDC operates with funding from a variety of sources, including Canadian Blood Service (CBS) and Quebec Blood Secretariat, who fund CHARMS, Health Canada who funds the BBP project, and a number of Pharmaceutical companies including Baxter, Bayer, Wyeth, ZLB, and Novo Nordisk, who provide funding for annual meetings, inhibitor surveillance, the inhibitor lab, and a hemophilia dog colony. Baxter has promised funding for a Robot for automated aliquoting of samples.

Individual clinics are funded by provincial Departments of Health through a variety of mechanisms in 24 different centers around the country. The Canadian Hemophilia Society has been instrumental in lobbying provincial governments to continue funding of comprehensive care clinics across Canada. Multidisciplinary conferences in 1978 and 1998 established and updated standards of care for bleeding disorders in Canada. These recommendations can be found on the CHS and AHCDC websites: <http://www.ahcdc.ca/>, <http://www.hemophilia.ca/>

In 2003, Baxter BioSciences Canada agreed to provide financial support for AHCDC as a research network. Upon their request, the AHCDC approached the Canadian Institutes of Health Research for matching funds in June, 2004.

Within the Blood Borne Pathogens Surveillance Project we have collected the ethics applications for the major centers in Canada and have developed a process for supporting the investigators in the AHCDC by filling out REB applications and supporting their submission. This process has dramatically facilitated this project, and other projects.

The information system - Canadian Hemophilia Registry or CHR:

The archive uses the numbering scheme from Canadian Hemophilia Registry developed in the 1980's by Dr. Irwin Walker from Hamilton. This registry originated as a tool to follow survival of hemophilia patients, but has become the basis for product tracking, and the numbering scheme for the BBPSP. The CHR has been upgraded in the last year and now includes patients with all inherited bleeding disorders, including von Willebrands disease, platelet disorders, deficiencies of all described clotting factors. The current state of the registry can be seen at: <http://www.fhs.mcmaster.ca/chr/> . Data summaries are available at this site as pdf documents. Data on HIV positive patients is appended, other reports are available from the website as pdf files.

The information system – Canadian Hemophilia Assessment and Resource Management System or CHARMS:

In the late 1980s, Dr. Irwin Walker in Hamilton had the foresight to develop an anonymous registry of patients with bleeding disorders, known as McCHip. 1993, following the widespread introduction of recombinant Factor VIII treatment in Canada, the Canadian Blood Agency asked the AHCDC to develop a proposal for a management information system to track coagulation concentrates used in patient homes. The distributed database system, known as CHARMS (Canadian Hemophilia Assessment and Resource Management information System), was developed, tested, and launched throughout Canada over the next five years. This system was primarily designed to track coagulation concentrates for recall and outcomes assessment, but it has evolved into a complex medical management system and electronic chart, with export of non-nominal data to a central database known as CentrePoint.

Health Canada has supported the purchase of new computers, the funding of computing science students to set up the new computers, transfer data, and secure the old computers by overwriting data. Over the last year, programmers from the Blood Borne Pathogens division of Health Canada have reviewed the CHARMS program.

At present the greatest efforts are being expended on the exchange of data between CHARMS/CentrePoint, CBS, HQ, the Quebec Blood Secretariat and the computerized patient inventory systems developed by Baxter, Bayer, and NovoNordisk. All parties have agreed to exchange data. The biggest difficulty has been in establishing standardized data to exchange. All parties have now agreed, and data exchange will be trialed in 4 test sites in the summer of 2004.

The information system – BBP project database:

With funding from Health Canada, we have developed a secure database to track the samples in our tissue archive. This database is a robust and secure database, developed locally with Jason Badry. The key features of this database are:

1. It is an MS-Access database with added security, including strong encryption of key fields, and a password file that is separately encrypted. The security of the database does not rely on MS Access security.
2. Access to the computer operating system and the database are both password protected with a time-out after a programmable time of inactivity.
3. Passwords are generated, not stored as plain text within the source code.
4. Encrypted messages are padded with random information and “hashed” using standard MD5/CRC hashing to verify the integrity of the data.
5. Sensitive information is stored with strong encryption. i.e. Samples come to the BBP project labeled with a bar-coded Canadian Hemophilia Registry (CHR) Number, and no other demographic data. The CHR is then mapped to a unique patient number and an inventory number that are used throughout the database.
6. There is complete logging of activity with detailed searching / filtering of logged material.
7. There are comprehensive validations and checks throughout the database.
8. There are configurable alerts, messages, and voices, as well as the integrated barcode functions, allowing minimal keyboard interaction with the database. Physical locations of samples are graphically mapped for better understanding, and the sample, labeled with an inventory number, is matched to a specific location within the storage facility.
9. There is simple, robust, and duplicated back-up functions.
10. There are multiple pre-configured reports, including status of sample collection from individual clinics, status of samples, patient visits to local clinics, and searchable ID fields. Consent is collected within the database.

The archive:

The archive itself is a robust archive of processed blood samples, including plasma, DNA, RNA, and cells. The key features of the archive are:

1. Collection and transportation using standardized tubes, transport containers, and processing.
2. Collection of RNA in commercial PaxGene tubes optimized for RNA stability and integrity during transport and storage.
3. Transportation in secure/safe transport containers, and temperature protection to maintain room temperature using a unique phase-change system developed by SafetyPak for this project.
4. Storage of liquid samples in 0.5 ml polypropylene tubes, made specifically for this project by Axigen. Racks and storage boxes are similarly optimized to provide optimal storage, and are produced by Axigen for this project.
5. Storage of DNA samples as dried blood on ion exchange paper (FTA paper, from Whatman) for better stability.

A blood processing robot, in development by Ward Systems to automate the aliquoting of samples. This is being funded by Baxter BioScience.

4.0 Goals and Objectives

The network:

In 2002, the AHCDC applied to the Networks Centers of Excellence to be funded as a research network. This application was unsuccessful. In 2003, Baxter Corp offered funding, to be matched by CIHR, to establish such a network. At present, the group, under the leadership of Dr. Jean St. Louis, Dr. David Lillicrap, and Dr. Bruce Ritchie are negotiating with CIHR to formalize this arrangement. This funding will support a statistician, and national data manager.

Trevor Soll is currently employed 1/2 time through the BBP project. This year, his salary will be switched to the AHCDC, as he moves on to other collaborative research projects. He will continue to provide a national infrastructure to fill out REB applications, and support the BBPSP.

The information system - CHR:

The Canadian Hemophilia Registry has been upgraded in the last year and now includes patients with all inherited bleeding disorders, including von Willebrands disease, platelet disorders, deficiencies of all described clotting factors. As noted above, current state of the registry can be seen at:

<http://www.fhs.mcmaster.ca/chr/> . The CHR will continue to accrue patients who will then be approached regarding participation in this project.

The information system - CHARMS:

The next evolution of CHARMS will change the database from Access format to an SQL format, and move the program to a web-based program. This will require the amalgamation of data from the distributed database that makes up CHARMS, into a central, secure, database in which access to data is limited to the patients managed by individual clinics. The assurance of privacy

protection and freedom of information is a bigger challenge than the technical side of this proposal.

Health Canada has agreed to provide programming help through Nick Karitsiotis to carry out this change in format. This will be done in collaboration with CBS, Hema Quebec, and the companies providing electronic product tracking (Bayer, Baxter, and NovoNordisk).

The information system - BBP:

The BBP database is secure, robust and functioning well. The database is secure; there is no connection to the internet, it is backed up frequently to an offsite storage area, and the room is locked. Electronic locks and webcam-based surveillance of the space are in development. The database is robust in that it uses barcodes wherever possible to minimize the chance of keyboard errors, and uses voiced data to direct archive technicians wherever possible. Health Canada has agreed to provide help through Nick Karitsiotis to provide a tool for data entry for tests done through BBP into a web-based CHARMS interface.

The archive:

The archive itself is a robust archive of processed blood samples, currently growing at a logarithmic rate as clinics come on-line. It is expected that sample procurement will plateau in about three or four years time. Baxter Corp has agreed to provide a robot for automated sample processing through a lease to own agreement.

Funding is required to maintain the project according to the attached budget (\$200,000/year). It is expected that as other rare blood disorder clinics become established, more funds will be required to collect these samples.**Project Plan**

Clinic Network:

Continued negotiation between Baxter, AHCDC, and CIHR will formalize the research network. An application for matching funds has been made to CIHR, and is pending.

The information system - CHR:

CHR will continue to accrue patients, particularly into the rare bleeding disorder registry. While the Hemophilia data is fairly mature, accrual of data in the von Willebrand's and Rare Bleeding Disorder registries is continuing as these patients are registered in the clinics.

The information system – CHARMS database:

With support from Health Canada, CHARMS will be migrated to SQL server, and a web-based program with data entry modules to the investigators using BBP samples. Nick Karitsiotis from Health Canada has been provided with the CHARMS program and has agreed to provide technical help in converting the program to a web-based program.

The information system – BBP database:

Health Canada has agreed to provide help through Nick Karitsiotis to provide a tool for data entry for tests from the BBPSP into a web-based CHARMS interface.

The archive:

The archive is expected to continue to grow, as samples accrue for bleeding disorders, and as samples are added for other disorders requiring blood products for treatment (Primary Immune Deficiency, Hereditary AngioEdema, Sickle Cell Disease, Thalassemia). Funding is requested to continue the accrual of samples from the Bleeding Disorder population, while funding is being sought from elsewhere to support collection of samples from patients with other rare blood disorders that require blood products. Predicted growth of sample accrual is shown in Figure 1 and Figure 2 below. These are updated regularly on the BBPSP website at: <http://www.ahcdc.ca/images/FreezerUpdate.gif> and <http://www.ahcdc.ca/images/Clinic%20update060104.gif> We expect to double the size of the archive this year (1200 patient visits) and then double it again the following year (2400 patient visits). This is a conservative estimate based solely on the Bleeding Disorder population. If funding comes through for Immunodeficiency patients and AngioEdema patients, this will grow even faster.

Salaries: Funding is required for the salary of Dr. Jonathan Hooton, laboratory director of the BBPSP until March 31 2005. Dr. Hooton is planning to move to another project at that time. Funding is then requested for a full time technician to replace him. Funds will be needed for an overlap period with Dr. Hooton.

Equipment: Funding is needed for one large liquid nitrogen dewar. The current freezer is 1/2 full. With the current acceleration of sample accrual, we will need to consider moving to a higher capacity system, likely based on liquid nitrogen at the end of this funding period. The current budget will not cover this, so we are seeking funding elsewhere. We are collaborating with the Centers for Disease Control in Atlanta on the design and development of automated sample storage in liquid or vapor phase nitrogen.

Supplies: Funding is requested for supplies for the Central Lab, as outlined in the attached budget spread sheet, including disposables for the robotic aliquoting system, and reagents.

Sample Collection: Funding is requested for continued sample collection. Support for obtaining consent, collecting blood samples, and shipping is requested.

Appendix B

Association of Hemophilia Clinic Directors of Canada
 Blood Borne Pathogens Surveillance Project
 April 1, 2004 – March 31, 2006

BUDGET

	Quarterly 2004-5	Annual (Apr.1/04-Mar.31/05)	Quarterly 2005-6	Annual (Apr.1/05-Mar.31/06)
Salaries and Office Expenses				
Office Costs(stamps, telephone, fax charges)	\$860.63	\$3,442.50	\$155.63	\$622.50
Salaries				
Laboratory Director - Hooton	\$15,750.00	\$63,000.00	\$3,937.50	\$15,750.00
Technician	\$3,750.00	\$15,000.00	\$7,875.00	\$31,500.00
Training TDG		\$430.00		\$450.00
ISBER		\$2,400.00		\$2,500.00
Subtotal Salaries & Office Expenses	\$20,360.63	\$84,272.50	\$11,968.13	\$50,822.50
	\$84,272.50		\$50,822.50	
Database				
Programming/maintenance		\$5,000.00		
Sample Collection				
Consent, sample collection, data collection (\$50.00/pt/yr)	\$10,625.00	\$42,500.00	\$21,250.00	\$85,000.00
Courier Costs (\$60/shipment. Appx. 36 shipments/yr)	\$1,500.00	\$6,000.00	\$3,000.00	\$12,000.00
Shipment Return (estimated at \$10.00/shipment/year)	\$450.00	\$1,800.00	\$600.00	\$2,400.00
Shipping Supplies	\$270.00	\$1,080.00	\$360.00	\$1,440.00
Subtotal Sample Collection	\$12,845.00	\$51,380.00	\$25,210.00	\$100,840.00
	\$51,380.00		\$100,840.00	
Central Laboratory				
0.5 ml tubes		\$14,000.00		
6 ml vacutainer	\$630.00	\$2,520.00		
paxgene tubes	\$5,619.38	\$22,477.50	\$5,619.38	\$22,477.50
FTA card	\$1,320.00	\$5,280.00	\$2,640.00	\$10,560.00
labels	\$337.50	\$1,350.00	\$675.00	\$2,700.00
supplies	\$3,000.00	\$12,000.00	\$3,150.00	\$12,600.00
Filing Cabinet for FTA cards		\$1,680.00		
Bins for FTA cards		\$40.00		
Subtotal Central Laboratory Budget	\$10,906.88	\$59,347.50	\$12,084.38	\$48,337.50
	\$59,347.50		\$48,337.50	
TOTALS				
Salaries and Office Expenses	\$20,360.63	\$84,272.50	\$11,968.13	\$50,822.50
Database		\$5,000.00		\$0.00
Sample Collection	\$12,845.00	\$51,380.00	\$25,210.00	\$100,840.00
Central Laboratory	\$10,906.88	\$59,347.50	\$12,084.38	\$48,337.50
Quarterly Expenses Subtotal	\$44,112.50		\$49,262.50	
BBPSP TOTAL		\$200,000.00		\$200,000.00

**Association of Hemophilia Clinic Directors of Canada
Blood Borne Pathogens Surveillance Project
April 1, 2004 – March 31, 2006**

REPORTING PLAN

Date	Report
March 31, 2005	2004-5 Final Report
September 30, 2005	Interim Report
March 31, 2006	2005-6 Final Report

**Association of Hemophilia Clinic Directors of Canada
Blood Borne Pathogens Surveillance Project
April 1, 2004 – March 31, 2006**

CASHFLOW FORECAST

Time Frame	Payment Schedule	Project Activities
October 1, 2004	\$100,000	
December 31, 2004	\$ 60,000	Interim Report
March 31, 2005	\$ 40,000	Interim Report
April 30, 2005	\$ 50,000	
September 30, 2005	\$ 50,000	Interim Report
January 1, 2006	\$ 60,000	
March 31, 2006	\$ 40,000	Final Report
Total	CDN\$400,000.00	