‘B Positive’ Project
Improving community based diagnosis and treatment of chronic Hepatitis B
CLINICAL PROTOCOL
TITLE:
The ‘B Positive’ Project: Improving community-based diagnosis and treatment of chronic Hepatitis B in at-risk communities in NSW - a Cancer Council NSW Pilot Project

Protocol for a clinical study funded by The Cancer Council NSW

National Ethics Application Form
(submitted 30/01/2008)
Lock Code Number: AB/2345/1

RACGP National Research and Evaluation Ethics Committee
(submitted 14/01/2008)
code 08/001)

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Original version 5th September 2007
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The CCNSW “B Positive Project” Coordinating Investigator will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of reported data and analyses in cooperation with the Principal Investigators. All methodological questions should be addressed to the Coordinating Investigator.

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‘B Positive’ Project
Investigator Agreement and Signature Page

Between the CCNSW (the Sponsor) and the Investigators

Chief Investigator: Dr Monica Robotin & Principal investigators (listed below)

This study is aiming to optimize the follow up and treatment pathways for CHB infection and screening for hepatocellular carcinoma in at-risk populations in defined regions of Sydney. The study will enroll and follow up individuals with chronic hepatitis B infection recruited through general practice and pathology records.

Participants will be offered comprehensive screening and assessment for chronic hepatitis B (CHB) infection and enrolment in a tailored CHB follow up program, based upon an algorithm that takes into account their age, presumed age at HBV infection, HBV viral load and liver function parameters. Participants will be enlisted into a GP-led ‘routine’ or ‘enhanced monitoring program using this algorithm, with the final decision on treatment algorithms resting with their treating physician. Participant enrollment is expected to start in March 2008. The signed consent forms will be forwarded by the GP to the Project Coordinator for enrolment of patients then retained by the Chief Investigator.

Relevant patient data will be extracted from patient and pathology records and entered into a specially designed Registry database, developed for this Project. Follow up visit data provided by general practitioners and specialist clinicians will be collected using a case record form completed at study visits and subsequently entered into the Registry database. Patient medical records will also be updated with regards to study information. The Registry will provide a reminder letter inviting participants to attend a review appointment for clinical monitoring follow up at 6 monthly intervals during the period of the study.

All patients will provide written informed consent for participating in the study.

I/We accept responsibility for the conduct of the research detailed in the proposal including all protocol-specific assessments, and I/We agree to abide by all decisions made by our Ethics Committee.
I/We agree to the above, which, in conjunction with the NHMRC Statement on Ethical Conduct in Research Involving Humans, will serve as the basis for co-operation in this study.

CHIEF INVESTIGATOR (signed & date) 
Monica Robotin

PRINCIPAL INVESTIGATORS (sign & date)
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Gregory Dore

Jacob George

Miriam Levy

Nghi Phung

Nicholas Zwar

COORDINATING INVESTIGATOR
Steven Tipper

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Ken Cho

Clinical Protocol v 5.0   Modified version date: 30 January 2008   Page 4 of 30
**TITLE**
The ‘B Positive’ Project: Improving chronic Hepatitis B diagnosis and treatment in the community - a Cancer Council NSW Pilot Project

**SPONSOR**
The Cancer Council NSW

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>Primary</th>
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<tr>
<td><strong>This pilot project aims to:</strong></td>
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<td>1. Determine if a primary-care based program of CHB screening and follow up among at risk populations (identified based upon their country-of-birth) is:</td>
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<td>(a) acceptable to individuals in the study population and</td>
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<td>(b) acceptable to their treating GPs,</td>
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<td>(c) economically feasible and</td>
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<td>(d) clinically effective</td>
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<td>in reducing the chronic disease burden (including hepatocellular carcinoma or HCC) in the target population.</td>
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<td>2. Inform Government policy and clinical practice recommendations for treatment of CHB infection among Australian residents born in countries with high endemicity of HBV infection.</td>
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**Secondary**

- To determine the costs of CHB diagnosis and optimized management in the pilot screening program covering specific LGAs and estimate how these findings can be extrapolated to inform State and National programs treating CHB.
- To determine success factors, enablers and barriers to engagement of General Practice, community organisations and at-risk individuals in enrolling in a program aiming to improve outcomes in chronic hepatitis B and liver cancer in a primary care setting
- To determine if the development of an expert-consensus screening and surveillance (clinical monitoring) protocol optimizes the diagnosis, treatment and referral processes for CHB patients from General Practice to clinical Specialists and enhance dialogue between clinical groups
- To determine whether age-specific cut-offs for specialist referral of HBV DNA >20,000 IU/ml for people aged 35 - 50 years and >2,000 IU/ml for those aged > 50 are appropriate for HCC screening and consideration of antiviral treatment initiation in an Australian context.
- To determine the most appropriate cut-off value/s for alanine aminotransferase (ALT) as a biochemical marker of liver damage and its utility as an indicator for initiating treatment for HBV infection in an Australian context;
- To develop a database that will support further research into the pathophysiology and clinical outcomes in people with chronic hepatitis B attending primary care and tertiary level clinics.
**STUDY DESIGN & INTERVENTIONS**

This is a prospective longitudinal cohort study of people with CHB who will be followed up for a period of up to three years, with the frequency of follow up dictated by a clinical algorithm taking into account their disease severity and potential risk of HCC development. The participant’s usual medical provider will make determinations about recommended type of follow up and treatments. Sites will be required to routinely provide data to the B Positive Project Registry.

**DURATION OF STUDY**

Planned study period of 3 years ending 2010. (NSW &/or Commonwealth funding of program roll-out may extend the project beyond this date for a further period).

**NUMBER OF SUBJECTS**

It is estimated that the study will recruit and follow up approximately 3,000 patients.

**STUDY SITES**

Primary and tertiary care sites in Sydney South West and Sydney West Area Health Services. We estimate 50 general practices from the Sydney South West General Practice Network will be participating in this program. The tertiary care centres affiliated with the program include: Liverpool, Bankstown and Westmead Hospitals.

**TARGET POPULATION**

Men and women ≥35 years old, identified as having chronic hepatitis B infection, based upon GP and pathology records. It is estimated that the majority of these patients will be known to their general practitioners, but some new diagnoses are likely to occur, in patients from at risk groups not previously tested for HBV infection.

**SELECTION CRITERIA**

Eligibility

Individuals (males an females) aged ≥ 35 and born in countries where HBV infection is endemic (in particular Vietnam, China, Hong Kong, the Philippines) plus other Australian residents who attend a general practice in the target area (Sydney South West and Sydney West) who meet the following criteria:

Inclusion Criteria:

- Confirmed CHB (persistent HBsAg positivity for >6 months)
- Have given informed consent to participate in the study

**PRIMARY ENDPOINTS**

Bi-annual reports documenting the proportion and demographic and clinical characteristics of participants:

- Undergoing routine clinical monitoring
- Referred for specialist assessment (including reasons for referral)
- Offered treatment for CHB infection
- Offered HCC screening - and number of HCC diagnosed
- Proportion of complete/ incomplete follow up and reasons for program discontinuation

**SECONDARY ENDPOINTS**

- Proportion of patients achieving HBV clearance
- Adherence to treatment (if treated)
- Toxicity of treatment (if treated)

**STATISTICAL ANALYSES**

Tabulations of participants by demographic and clinical parameters, univariate analysis of risk factors for progression/ HCC development/ HBV clearance, and viral load level.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ii INVESTIGATORS INFORMATION</td>
<td></td>
</tr>
<tr>
<td>Study investigators</td>
<td>2</td>
</tr>
<tr>
<td>Investigator Agreement and Signature Page</td>
<td>4</td>
</tr>
<tr>
<td>iv STUDY SYNOPSIS for the ‘B Positive Project’</td>
<td>5</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>7</td>
</tr>
<tr>
<td>1.0 Purpose of Study</td>
<td>8</td>
</tr>
<tr>
<td>1.1 Primary Objectives</td>
<td></td>
</tr>
<tr>
<td>1.2 Secondary Objectives</td>
<td></td>
</tr>
<tr>
<td>2.0 Background and rationale</td>
<td>9</td>
</tr>
<tr>
<td>2.1 Summary</td>
<td></td>
</tr>
<tr>
<td>2.2 Epidemiology of HBV infection in Australia</td>
<td></td>
</tr>
<tr>
<td>2.3 The clinical epidemiology of liver cancer in NSW</td>
<td></td>
</tr>
<tr>
<td>2.4 Therapeutic Options for CHB Management</td>
<td></td>
</tr>
<tr>
<td>2.5 Screening for HCC</td>
<td></td>
</tr>
<tr>
<td>3.0 Study Design</td>
<td>13</td>
</tr>
<tr>
<td>3.1 Overview of study design</td>
<td></td>
</tr>
<tr>
<td>3.2 Recruitment of study participants</td>
<td></td>
</tr>
<tr>
<td>4.0 Study population</td>
<td>14</td>
</tr>
<tr>
<td>4.1 Target population</td>
<td></td>
</tr>
<tr>
<td>4.2 Patient selection criteria</td>
<td></td>
</tr>
<tr>
<td>5.0 Study procedures</td>
<td>16</td>
</tr>
<tr>
<td>5.1 Identification and recruitment of potential study participants</td>
<td></td>
</tr>
<tr>
<td>5.2 Laboratory and clinical investigations</td>
<td></td>
</tr>
<tr>
<td>6.0 Data collection, Source Documents and Record Retention</td>
<td>21</td>
</tr>
<tr>
<td>6.1 Data collection</td>
<td></td>
</tr>
<tr>
<td>6.2 Source data</td>
<td></td>
</tr>
<tr>
<td>6.3 Record retention</td>
<td></td>
</tr>
<tr>
<td>7.0 Ethics Committee/Regulatory Approval and Informed Consent</td>
<td>22</td>
</tr>
<tr>
<td>8.0 Confidentiality of data</td>
<td>25</td>
</tr>
<tr>
<td>8.1 Confidentiality of patient records</td>
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<tr>
<td>8.2 Confidentiality of study data</td>
<td></td>
</tr>
<tr>
<td>9.0 Financing &amp; Insurance</td>
<td>26</td>
</tr>
<tr>
<td>10.0 Publications policy</td>
<td>27</td>
</tr>
<tr>
<td>References</td>
<td>28</td>
</tr>
<tr>
<td>Glossary of abbreviations</td>
<td>30</td>
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</table>
1.0 Purpose of the study

The study aims to test the feasibility, acceptability, and cost-effectiveness of a GP-led hepatitis B screening and clinical monitoring (sometimes called “surveillance”) program in individuals with chronic hepatitis B infection and who are at high risk of developing liver cancer. The project will be instrumental in determining the role targeted HBV screening and clinical monitoring plays in preventing end-stage complications of CHB.

The project seeks to increase detection of chronic hepatitis B (CHB) infection and ensure regular follow up and optimize treatment of people with CHB infection, by facilitating timely and appropriate referral for hepatitis treatment. In addition, the program will screen at risk individuals for liver cancer, aiming to increase the proportion of people whose disease is diagnosed early, at a stage where it may be amenable to curative interventions.

The pilot project will screen, detect and treat chronic hepatitis B (CHB) infection and facilitate regular follow up to assist in the early detection and treatment of hepatocellular carcinoma (HCC) and its sequelae. Data from the project will be analysed to estimate the costs of HBV management within the pilot screening program on a targeted LGA basis to inform recommendations to Government on policy at NSW State and National levels.

1.1 Primary Objectives (see table)

1.1.1 Determine if a primary-care based program of HBV screening and follow up among at risk populations (identified based upon their country-of-birth) is:

(a) acceptable to individuals in the study population

(b) acceptable to their treating GPs,

(c) economically feasible and

(d) clinically effective

in reducing the chronic disease burden of CHB in the target population.

1.1.2 Inform Government policy and clinical practice recommendations for the treatment of CHB infection among Australian residents born in countries with high endemicity of HBV infection.

1.2 Secondary Objectives

1.2.1 To estimate how the costs of HBV management within the pilot screening program on a targeted LGA basis can be extrapolated to inform State and National programs treating CHB;

1.2.2 To determine success factors, enablers and barriers to engagement of General Practice, community organisations and at-risk individuals in a program aiming to improve outcomes in chronic hepatitis B and liver cancer in a primary care setting; [Note: this will include sub-objectives such as: identifying the need for GP educational resources supporting improved hepatitis B diagnosis and management; identifying and documenting the need for targeted development and evaluation of...
1.2.3 To determine if the development of an expert-consensus screening and clinical monitoring protocol optimizes the diagnosis, treatment and referral processes for CHB patients from General Practice to clinical Specialists and enhances dialogue between these groups;

1.2.4 To test whether age-specific cut-offs for specialist referral of HBV DNA > 20,000 IU/ml for people aged 35 - 50 years and > 2,000 IU/ml for those aged > 50 are appropriate for HCC screening and consideration of antiviral treatment initiation in an Australian context;

1.2.5 To determine the most appropriate cut-off value/s for alanine aminotransferase (ALT) as a biochemical marker of liver damage and its utility as an indicator for treatment for HBV infection in an Australian context;

1.2.6 To develop a database that will support investigation by clinical researchers of relevant information about patients with chronic hepatitis B attending primary care and tertiary level clinics. [Note: includes, for example, data collection to support patient recall to GPs and Specialist clinical services, reporting on project and patient outcomes and determination of the prevalence rates for CHB in the target population in SSWAHS (by age, sex, COB, ethnicity, immigration year, GP attendance history, marriage status)]

2.0 Background and rationale

2.1 Summary

Over the last 2 decades the incidence of liver cancer in NSW has been increasing faster than any other internal cancer. In NSW liver cancer exhibits a striking pattern of geographic clustering, with the highest rates of primary liver cancer occurring in South Western Sydney, where the incidence of liver cancer (12.1 per 100,000) far exceeds the NSW state average (of 4.8 cases per 100,000 persons).

Hepatocellular carcinoma (HCC) represents approximately 90% of all liver cancers but as Cancer Registry data do not differentiate HCC from other types of primary liver cancer, this paper refers to HCC and primary liver cancer interchangeably. Traditionally HCC has been diagnosed in advanced stages, when prognosis is uniformly poor, but as evidence increasingly suggests that earlier detection leads to improved outcomes, this has ignited the debate about the relative merits of earlier detection through liver cancer screening.

Worldwide over 80% of liver cancer is attributable to the combined effects of chronic hepatitis B and C infections, with infected individuals having a 20 to 100-fold increased risk of developing HCC relative to those uninfected. Liver cancer occurs most frequently in Eastern Asia, Middle Africa and some countries of Western Africa, with estimated age-adjusted incidence rates in men being approximately 10 times higher in Eastern Asia, compared to that in Australia/New Zealand.

The high incidence of liver cancer in Asia is due to the high prevalence of chronic viral hepatitis, particularly chronic hepatitis B. In countries where HBV infection is endemic, the disease is contracted early in life (either perinatally or in early childhood),
whereupon the lifetime risk of developing chronic HBV infection is very high (>60%), with 15-40% of chronically infected people at risk of developing cirrhosis, liver failure or liver cancer over their lifetime.7

The demonstration of a close correlation between HBV replication and the risk of disease progression and liver cancer,8-10 coupled with data suggesting that effective suppression of viral replication may be associated with a reduced risk of HCC,8-11 may represent a paradigm shift in HCC prevention strategies, provided that issues around antiviral resistance, treatment cost and duration can be satisfactorily addressed.

2.2 Epidemiology of HBV infection in Australia

HBV infection is a Notifiable disease (by doctor and/or laboratory) in all Australian State and Territory Health jurisdictions, with 5000-6000 annual notifications received by the Commonwealth Government’s National Notifiable Diseases Surveillance System (NNDSS) for collation and national reporting. These National hepatitis B notifications provide sparse data for specific analysis at the individual patient level, excluding for example the country of birth and Indigenous status or ethnicity of the patient. 12

The number of chronic hepatitis B virus (HBV) infections in Australia has been estimated to range between 91,000-163,000 (with the wider range of estimates reflecting the uncertainty in the available source data), representing a population prevalence range of 0.49% to 0.87%.13 CHB prevalence is significantly higher in overseas-born individuals, with a hospital-based case series finding that among people born overseas, the odds of CHB infection were 12.4 for people born in Asia/ Pacific Islands and 6 for those if born in North Africa, Middle East and Mediterranean countries.14

Likewise, overseas-born people are at a significantly increased risk of developing HCC compared to Australian-born individuals. The early age of infection in Asian patients accounts for significant differences in the clinical course of disease (the prolonged immune tolerance phase setting the scene for long-term complications) compared to Caucasians (who generally contract the disease late and enter the immune clearance phase soon after developing CHB), which may explain the latter group’s better prognosis and response to treatment.15

2.3 The clinical epidemiology of liver cancer in NSW

The Cancer Incidence in New South Wales Migrants 1991-2001 report demonstrated that although overall cancer incidence rate in overseas-born individuals was similar to that of Australian-born residents (24.5%), cancer profiles varied by migrants’ country of birth.16 A larger than expected proportion (46%) of all primary liver cancers occurred in overseas-born people, with males born in Vietnam, Hong Kong, Macau, Korea, Indonesia and China and females born in Vietnam and China being 6-12 times more likely to develop primary liver cancer than Australian-born individuals.16

Data from Westmead and Royal Prince Alfred Hospitals, (1997 to 2005) suggest that HCC can be diagnosed earlier and be associated with better survival in patients having regular screening.17 The update of this hospital-based case-series identified 712 cases of liver cancer to the end of 2006. The mean age at diagnosis was 58 years (range 17-85), with over one third of all cases (39%) diagnosed in Asian people.18 Aetiological factors included HCV in 35%, chronic HBV infection in 34 %, and a small proportion (3.5%) due to HBV and HCV coinfection.18 More than 90% of cases presented with
'B Positive' Project

cirrhosis and 3-year median survival was 43%, being higher in Asians (48%) than in Caucasians (39%). The most powerful predictors of survival were the alpha-fetoprotein (AFP) level at diagnosis and detection through screening rather than symptomatic presentation.\(^\text{18}\)

A case-series of people diagnosed with HCC at Liverpool Hospital from 1993 to 2003 identified 151 patients, with a median age at diagnosis of 68 years.\(^\text{19}\) Similar to the Westmead and Royal Prince Alfred Hospitals series, the proportion of Asian-born people was substantial (41%), 46% of all cases had chronic HBV infection and 26% had HCV infection. Over half the cases presented with cirrhosis (58%), most patients (75%) were symptomatic and the median survival was 5.1 months.\(^\text{19}\) In multivariate analysis detection by surveillance, lower Child-Pugh score, smaller tumour size and treatment eligibility were associated with better outcomes.\(^\text{19}\)

2.4 Therapeutic Options for CHB Management - Antiviral therapy for HBV infection

There are a limited number of antiviral therapeutic agents available in Australia with proven efficacy in the treatment of CHB. Interferon alpha (IFN) antiviral therapy has proven benefits for patients who respond to this therapy, with prolonged clinical remission and an increased rate of HBsAg seroconversion and improved liver histology, which indicate that after correction for baseline factors, response to IFN therapy increases survival and reduces the risk of developing HCC.\(^\text{20}\) Lamivudine, entecavir and adefovir are nucleoside analogues that have been used in the treatment of HBV.\(^\text{21}\) A recent Cochrane protocol review summarises the literature regarding CHB drug therapy and proposes the development of a protocol for the use of entecavir in this population, as there is no current systematic review or meta-analysis that evaluates the beneficial and harmful effects of entecavir for patients with chronic hepatitis B.\(^\text{22}\)

It is proposed in this study that the selection of appropriate therapy be ‘usual practice,’ so that the participant’s usual medical provider determines the appropriate treatment regimens. The algorithm for patient selection, follow up and surveillance does not prescribe a specific treatment protocol to be adhered to by the GP or the Specialist beyond their normal practice. The primary role of the Registry is as a repository of clinical data pertaining to the enrolled participants and to provide a patient/GP clinical monitoring reminder service.

2.5 Screening for HCC

2.5.1 Primary Prevention

The most effective and practical modalities to controlling HBV infection and its long-term sequelae are primary prevention approaches, which aim to reduce or eliminate viral transmission. Key interventions include universal vaccination against HBV, ensuring a safe blood supply (through screening blood donations) and harm minimisation. Within 15 years from the commencement of mass immunization against HBV in Taiwan (1985), the carrier rate in children had decreased from 9.8 % to 0.7% \(^\text{23}\) and was paralleled by a reduction in the incidence rate of HCC in children aged 6-14.\(^\text{24}\) However, due to the long latency period and the large burden of undiagnosed disease in the community, a significant impact in reducing morbidity and mortality from liver disease is not expected for 30 or more years. Experts of the Hepatitis Control
Committee in Taiwan estimate that vaccination would eventually result in 80-85% decreases in the incidence of HCC in all adults within 3-4 decades.25

2.5.2 Secondary Prevention

Secondary prevention aims to reduce the proportion of people progressing to end stage liver disease and HCC by optimising their medical management. A screening strategy, taking into account the level of viral load has been suggested by the REVEAL study, which demonstrated that an elevated serum HBV DNA level (>10,000 copies/mL or approximately >2x10^4 IU/ml using the newer terminology) is a strong predictor of HCC risk, independent of other markers of activity, such as HBeAg, ALT or the presence of cirrhosis.26

Traditional screening regimes for the detection of HCC have included alpha-fetoprotein (AFP) and liver ultrasound, commonly used together, in order to improve screening accuracy, as their individual sensitivity and specificity is relatively low, particularly among people with cirrhosis.27 Patients with abnormal screening tests generally need additional workup, which may include CT scanning, MRI or liver biopsy.28 As negative screening results cannot reliably exclude the presence of a HCC, regular follow-up (generally at 6 months intervals) is recommended.29

The rationale for HCC screening is based upon the assumption that high-risk populations (such as those with HBV-related cirrhosis) can be identified, but as tumors can occur in livers with minimal histological changes, this limits the potential applicability of screening if the presence of cirrhosis is used to define the target population for HCC screening.30

One randomized controlled trial (RCT), enrolling over 18,000 people with chronic hepatitis B infection demonstrated a 37% reduction of mortality in people screened for HCC,31 but so far there is no consensus on whether screening with AFP or AFP/US improves mortality for HCC or not.32 33 However, due to the very low cure rate for symptomatically diagnosed HCC (5-year survival rates less than 10%), informal screening is widely practiced, as a means to increase the proportion of cancers amenable to liver resection or liver transplantation.27

Population-based HCC screening is not currently practiced in Australia, although some experts recommend it in high risk groups, such as Asian-born males over the age of 40, Asian-born females over the age of 50, African-born people over the age of 20, those with CHB-related cirrhosis, irrespective of age, and those with a family history of primary liver cancer.34

2.5.3 A new paradigm in screening for HCC

The demonstration of a close correlation between HBV replication and the risk of disease progression and liver cancer,8-10 coupled with data suggesting that effective suppression of viral replication may be associated with a reduced risk of HCC,8-11 may represent a paradigm shift in HCC prevention strategies, provided that issues around antiviral resistance, treatment cost and duration can be satisfactorily addressed. It can therefore be argued that the earlier detection of CHB can lead to optimized disease management, including timely initiation of antiviral therapies (if and when required) and be associated with improved outcomes. In the context of new and rapidly changing information about optimal management strategies for CHB, treatment benefits are more likely to accrue through participation in a formal screening and treatment program than
‘B Positive’ Project

by awaiting dissemination of new information through the usual GP-specialist communication pathways. Additionally, the aggregation of a large volume of clinical data in the target patient population can inform the development of treatment protocols more likely to be successful, acceptable and cost effective and lead to improved communication between primary care providers and clinicians. The latter point is the key contribution the program can make in optimizing patterns of care for CHB.

There is evidence that the incidence of liver cancer is increasing over time as shown in the historical upwards trend in New South Wales. The burden of CHB and liver cancer in Australia is likely to increase significantly in the future, due to the large population at risk, changing patterns of immigration and the long time period for progression from chronic hepatitis B infection to development of liver cancer.

The clustering of HCC cases in NSW along geographical and ethnic lines provides opportunities for devising targeted public health interventions to address the burden of disease associated with CHB, end-stage liver disease and liver cancer. Information on CHB prevalence by country of birth allows the identification of target populations who are likely to benefit most from enrollment in a cancer prevention and early detection program.

3.0 Study Design

3.1 Overview

This is an observational study in which data will be collected both retrospectively and prospectively. No treatments will be assigned as part of the study. All participating clinicians will be made aware of a treatment algorithm developed by local hepatitis B experts, which reflects the current recommendations of local and international expert reference groups, but all patient management decisions, including antiviral treatment and general clinical care will be at the discretion of their usual care provider.

Patient data will be recorded via participating clinicians and pathology service providers and entered into a project data base developed by the CCNSW in collaboration with investigators from Westmead Hospital, Sydney.

Approximately 2,000 patients are expected to be recruited for this study over the first two years, with additional recruitment in year 3 dependent on mid-point statistical and service delivery outcomes review. There is no randomisation or blinding.

3.2 Recruitment of study participants

Individuals with known chronic hepatitis B infection will be identified by retrospective case-finding using pathology service HBV test results aggregated at GP level. Review of these patient lists by individual GPs to determine HBV status (acute episode or chronic disease) and clinical sequelae (disease stage) will be followed by invitation of potentially eligible patients to enroll in the program. Information supporting recruitment will be provided in culturally appropriate ways through a community-based communication strategy. Formal consent to participate will be mediated via the patients’ GP, with resources translated in the relevant languages, as well as English.

Patients will be enrolled initially via two closely aligned Divisions of General Practice (Fairfield-Liverpool area), located within South Western Sydney Area Health Service.
‘B Positive’ Project

Agreement to participate in the study will be sought from individual GPs, who will be invited to recruit patients meeting the selection criteria. It is anticipated that approximately 50 primary care (General Practices) sites within the Divisions will participate over a period of two years, to achieve a target recruitment of 2000 patients.

Clinical Specialists from Liverpool, Bankstown and Westmead Hospitals involved in the treatment of CHB patients referred to their existing clinics by the participating GPs will be made aware of the program and may also consider recommending enrolment of eligible patients in the program, via the referring GP. Pathology results of patients enrolled in the screening and clinical monitoring project will be reported to their GP & Specialist as per normal practice, with data also captured via the project database.

Further details on procedures for recruitment of study subjects are given in section 5.1.

4.0 Study population

4.1 Target population

In NSW liver cancer exhibits a striking pattern of geographic clustering, with the highest rates of primary liver cancer documented in South Western Sydney. In this region, which includes the Fairfield, Liverpool, Bankstown and Canterbury Local Government Areas, the incidence of liver cancer (12.1 per 100,000) far exceeds the NSW state average (of 4.8 cases per 100,000 persons). ²

The Country of Birth Report found that males born in Vietnam, Hong Kong, Macau, Korea, Indonesia and China and females born in Vietnam and China are 6-12 times more likely to develop primary liver cancer than Australian-born individuals,16 underscoring the need to target the program to these groups and to areas where migrants born in these countries represent a significant proportion of the population.

We estimated the size of the target population for the hepatitis B screening and surveillance pilot project by using the Census 2001 and 2006 data for country-of-birth and place of residence location within South Western Sydney by Local Government Area (LGA) and by using estimated CHB prevalence rates derived from published local and international data.

Table 1 reflects the concentration of migrants at high risk of chronic hepatitis B and liver cancer in the selected LGAs. Immigrants from Viet Nam and China (both countries where Hepatitis B infection is endemic) represent a significant proportion of the total population in these LGAs and are the population most at-risk of chronic hepatitis B disease and future liver cancer.

This data supports the rationale for promoting the program in these communities and focusing recruitment primarily on these ethnic communities.

Table 1 identifies the population data for Country-of-Birth by Local Government Area in the South Western Sydney area (Major countries by number of migrants in each LGA, and cumulative percentage (%) of total LGA population [Census 2001 data])
‘B Positive’ Project

Table 1: Country-of-Birth by Local Government Area population

<table>
<thead>
<tr>
<th>Ethnicity / LGA</th>
<th>Vietnam (excl HK)</th>
<th>China</th>
<th>Italy</th>
<th>New Zealand</th>
<th>Philippines</th>
<th>Fiji</th>
<th>Korea (South)</th>
<th>Lebanon</th>
<th>LGA Population TOTAL</th>
<th>Cumulative % of LGA Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fairfield</td>
<td>24,937 (13.7%)</td>
<td>4,719 (2.6%)</td>
<td>5,341 (2.9%)</td>
<td>1,938 (1.1%)</td>
<td>2,291 (1.3%)</td>
<td>1,421</td>
<td>-</td>
<td>2,178 (1.2%)</td>
<td>181,937</td>
<td>24.7%</td>
</tr>
<tr>
<td>Liverpool</td>
<td>4,195 (2.7%)</td>
<td>1,548 (1.0%)</td>
<td>3,299 (2.1%)</td>
<td>2,385 (1.5%)</td>
<td>2,888 (1.9%)</td>
<td>4,509</td>
<td>-</td>
<td>3,035 (2.0%)</td>
<td>154,287</td>
<td>14.2%</td>
</tr>
<tr>
<td>Bankstown</td>
<td>9,743 (5.9%)</td>
<td>3,828 (2.3%)</td>
<td>2,289 (1.4%)</td>
<td>2,323 (1.4%)</td>
<td>1,069 (0.6%)</td>
<td>-</td>
<td>1,099 (0.7%)</td>
<td>10,647 (6.4%)</td>
<td>165,611</td>
<td>18.7%</td>
</tr>
<tr>
<td>Canterbury</td>
<td>4,711 (3.6%)</td>
<td>8,286 (6.3%)</td>
<td>2,940 (2.2%)</td>
<td>2,139 (1.6%)</td>
<td>2,001 (1.5%)</td>
<td>-</td>
<td>3,128 (2.4%)</td>
<td>7,552 (5.8%)</td>
<td>130,953</td>
<td>23.5%</td>
</tr>
<tr>
<td>Auburn</td>
<td>3,413 (6.1%)</td>
<td>4,536 (8.0%)</td>
<td>-</td>
<td>-</td>
<td>1,253 (2.2%)</td>
<td>1,003</td>
<td>2,434 (4.3%)</td>
<td>56,373 (10.7%)</td>
<td>689,161</td>
<td>22.4%</td>
</tr>
<tr>
<td>Subtotal (n)</td>
<td>46,999</td>
<td>22,427</td>
<td>13,869</td>
<td>8,785</td>
<td>9,502</td>
<td>5,930</td>
<td>5,230</td>
<td>25,846 (2.2%)</td>
<td>689,161</td>
<td>20.1%</td>
</tr>
</tbody>
</table>

Table 2 provides an estimate of the numbers of CHB cases in the five Local Government Areas among people born in countries of high HBV prevalence by age groups, assuming CHB incidence is consistent with that of their country-of-birth (COB).

Table 2: Target population estimate (Census 2006 data, assumed incidence ~ COB)

<table>
<thead>
<tr>
<th>Age band</th>
<th>Total population in area* 5 LGAs Sydney South West</th>
<th>Total sub-population born China, Vietnam or Hong Kong</th>
<th>Estimated Total CHB target population**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Males</td>
<td>Total Females</td>
<td>Total Males</td>
</tr>
<tr>
<td>35-44</td>
<td>58060</td>
<td>58730</td>
<td>9895</td>
</tr>
<tr>
<td>45-54</td>
<td>49682</td>
<td>49493</td>
<td>6091</td>
</tr>
<tr>
<td>55-64</td>
<td>32706</td>
<td>31801</td>
<td>2507</td>
</tr>
<tr>
<td>65-74</td>
<td>23002</td>
<td>24454</td>
<td>1989</td>
</tr>
<tr>
<td>75+</td>
<td>15497</td>
<td>23259</td>
<td>1036</td>
</tr>
<tr>
<td>Total age 35 and up</td>
<td>178947</td>
<td>187737</td>
<td>21517</td>
</tr>
<tr>
<td>Total age 35 and up both genders</td>
<td>366684</td>
<td>45015</td>
<td>8355</td>
</tr>
<tr>
<td>Total population, all ages</td>
<td>709904</td>
<td>80740</td>
<td>11720</td>
</tr>
</tbody>
</table>

* “Target” is residents from all countries of birth and Australia  ** Estimated CHB across all 5 LGAs (unpublished, CCNSW, November 2007)
4.2 Patient Selection Criteria

4.2.1 Eligibility

The program will be targeted to individuals (males and females) aged 35 years or older, with chronic hepatitis B, born in countries where HBV infection is endemic; Vietnam, China, Hong Kong, the Philippines-born individuals are the primary targets of this program. Additionally, other Australian residents who attend a general practice in the target area (Sydney South West and Sydney West) who meet the following criteria will be considered for inclusion:

4.2.2 Inclusion Criteria:

- Confirmed CHB (persistent HBsAg positivity for >6 months)
- Have provided written informed consent to participate in the study

4.2.3 Exclusion Criteria:

- Women with ongoing pregnancy or breast feeding (subject to Specialist review for antiviral drug treatment)
- History or evidence of other medical conditions associated with chronic liver disease, but no evidence of CHB (including, but not limited to: hepatitis C infection, drug or alcohol-related cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis, primary biliary cirrhosis, etc) that warrants exclusion as determined by their treating doctor.
- Inability or unwillingness to provide informed consent or abide by the requirements of the study (all subjects)

4.2.4 Criteria for Withdrawal of Patients

- Written withdrawal of consent should be obtained from any patient wishing to exit from the study
- All available study measures should be transferred to the CCNSW Registry database within a month of date of withdrawal.

5.0 Study Procedures

5.1 Identification & recruitment of potential participants

5.1.1 General Practice recruitment

Initial development of the pilot project in the Fairfield-Liverpool district in 2008 is based on the potential numbers of CHB cases in the target population (Tables 1 and 2 above) and mutual agreement reached between the CCNSW as Sponsor and the local Sydney South West General Practice Network Ltd (acting on behalf of the Fairfield and Liverpool Divisions of General Practice).

Medical practitioners in Sydney South West will be informed of the study through their local Division of General Practice. GPs will be invited to attend continuing professional development educational seminars and to participate in community information events.
Formal, written agreement from GPs to participate in the study will be required in addition to individual patient informed consent for people diagnosed with CHB.

Retrospective case-finding will be initiated by the Coordinating Investigator arranging for the pathology services normally used by a GP to provide a list of their patients who have had a past HBsAg positive result in the past (12 months up to a maximum of 3 years retrospective). The Chief Investigator will determine the suitability of patients for inclusion in the study and the Coordinating Investigator will notify the GP in writing (via email, fax or post) of the potential for enrollment and provide additional enrollment information or procedural guidance as needed.

From the retrospective HBsAg positive patients’ lists, each GP will verify that the patient is a current patient of their practice and contact them to arrange an appointment for a review of their past pathology test results, clinical examination and further testing to determine the current status of their infection. Patients meeting the selection criteria will be offered enrollment, with informed consent forms completion (refer Patient Information and Consent Form).

The completed Consent Form will be signed by the GP who will retain a copy for their records, while the original is forwarded to the CCNSW Project Officer for Registration. Following enrollment of the patient in the Registry a follow-up letter will be sent to the GP verifying the patients’ enrollment with a unique Study Participant Number, assigned by the Registry Database Manager, which will be the cross-reference for further communication and data management.

Prospective case-finding for CHB will be managed by GPs offering enrollment to patients who are identified as chronically infected after the study commences, provided they meet the study’s selection criteria.

5.1.2 Tertiary clinic site recruitment

The existing tertiary care hepatitis clinics in Sydney West and Sydney South West functioning as University teaching hospitals (Liverpool Hospital, Westmead Hospital and Bankstown Hospital) will also act as recruitment and follow-up sites for the project as they are the principal referral sites for at-risk patients from local GPs. Each of these hospitals is an existing treatment site for chronic hepatitis B and/or liver cancer and has senior clinical specialists who are Principal Investigators in the study.

Retrospective CHB &/or liver cancer case-finding from existing sources will be used for recruitment only if such patients can be recruited during a routinely scheduled follow-up visit, as would occur in the course of normal clinical practice (i.e., not requiring a special clinic visit).

5.1.3 Public health surveillance and pathology service recruitment

All public health service units within the study catchment areas will be notified of the study. Procedures will be developed in liaison with public health surveillance officers to enhance case finding and ensure previously identified CHB cases are considered by treating GPs for enrollment in the study.

It is expected that the current procedures for hepatitis B notifications will not change greatly as a result of patients’ enrollment in this study. In Sydney South West Area Health Service (SSWAHS), newly identified CHB infections notified to the public health
‘B Positive’ Project
unit (PHU) will be also be referred for inclusion in the GP-led screening program (contingent upon patient consent), as a first contact letter generated via the PHU or via the GP if notified directly by the pathology laboratory results. The SSWAHS PHU has experience in undertaking enhanced surveillance on notified cases of HBV infection to determine history of previous HBV testing, presence of chronic hepatitis and acute cases contact tracing. 35

The support of the PHU in providing educational advice to GPs enrolled in this study and contact follow up for new notifications may translate into a collaborative enhanced surveillance program coordinated with the CCNSW project. Such development is not currently part of this proposal and would be within the normal role of the PHU.

5.2 Laboratory and clinical investigations

5.2.1 Screening and clinical monitoring overview

Screening and clinical monitoring (sometimes referred to as ‘surveillance’) of patients post-enrollment will follow an expert-consensus algorithm developed for this project by the Steering Committee and other Advisory Committee experts, which takes into account recommendations of local and international reference groups treating CHB and liver cancer. This protocol streamlines patients into management pathways: GP-led routine or enhanced monitoring or specialist-led care, based upon the results of relevant laboratory investigations (see Diagram 1).

At first visit a general practitioner will perform a standard clinical assessment including the presence of symptoms or signs of chronic hepatitis &/or liver disease. Baseline information will be collected as identified below.

Baseline visit (GP)
- Inform patient of the relevance of the project to CHB care &
- Ensure informed consent is obtained
- Document baseline information.

Follow-up visits (GP & Specialist referral)
- Patients undergo treatment and/or assessment as per routine standard of care. A “screening and monitoring” algorithm provides guidance for additional follow up dependent upon laboratory results from the initial screening (Appendix 1) or changes in results while in the monitoring program (Appendix 2)
- Sites will forward required patient information and test results to the data centre on a regular basis (within a short period after patient recall visits) over the pilot project period.

Hospital clinic sites will continue to operate as per normal practice except for:
- The collection of blood &/or biopsy tissue for pathology tests on enrolled patients: The specimen/s will be identified to the pathology provider as a participant of this study. Storage of specimens (blood, including plasma, and tissues) with the pathology service will be arranged locally, followed by regular transfer of study specimens from the pathology lab to long-term storage hosted by Westmead Hospital. The Westmead Hospital storage of study specimen matter is agreed to be under the supervision of Prof J. George as the Principal Investigator responsible for keeping records of the management of specimens (including access to & maintenance of storage, testing, results etc) on behalf of the Sponsor;
5.2.2 Baseline variables to be recorded

1. Demographic / lifestyle
   - name
   - address
   - gender
   - date of birth
   - country of birth and/or ethnicity
   - estimated age at HBV infection
   - alcohol consumption
   - smoking history (a known risk factor for HCC)
   - drug use (including prescribed medications, complementary and alternative medications and illicit [recreational] drug use)
   - other risk factors (screening questions included in the Case Record Form)
   - GP contact details

2. Clinical / virological
   - clinical history including
     - co morbidities and
     - previous and current therapy for hepatitis B
   - clinical examination findings
   - suspected source of infection
   - HBV serology (HBsAg, HBeAg, anti-HBs, anti-HBc)
   - HIV serology (optional dependent on history)
   - HCV serology (if not previously tested & should be consistent with the National Hepatitis C Testing Policy May 2007)
   - liver function tests
   - Full blood count
   - basic body measurements (weight, height)

5.2.3 Follow up testing variables to be recorded

For enrolled patients diagnosed with CHB infection from the initial screening tests, the results of HBV DNA and ALT laboratory tests determine the 'level' of GP-led clinical monitoring or Specialist referral in accordance with the algorithm (Appendix 1 & 2).

The summary below identifies the tests most likely to be performed in an uncomplicated case. It may not reflect all the possible tests which a clinician is authorised to order in accordance with their normal clinical practice or to address individual patients ‘best-practice’ management due to comorbidities or other factors reliant on their expert knowledge or the requirements of providing services under a particular model of care.

Summary of follow up testing (CHB post-screening + HCC monitoring)
   - therapy changes since last visit,
   - side effects from any therapy
   - liver function tests and liver enzymes
‘B Positive’ Project

- full blood count (including Hb and platelet counts)
- HBV DNA assessments
- HCV RNA assessments (if previously known co-infection)
- new co-infections
- liver biopsy findings

The lists below group the expected investigations by ‘type’ of follow up & result:

Routine Monitoring Care (Inactive CHB)
- GP-led
- Six-monthly recall & review
- HBsAg
- ALT testing
- assessment for any symptoms of liver damage
- annual HBV DNA
- annual HBeAg testing for those who were previously HBeAg positive

Enhanced Monitoring Care (Active CHB, Normal ALT)
- GP-led oversight six-monthly including same testing as above plus
  - AFP test
  - Diagnostic imaging e.g., Ultrasound

Specialist referral (Active CHB, High ALT or abnormal AFP &/or US)
- Diagnostic imaging (e.g., Ultrasound or CT as ordered through specialists)
- Specialist oversight of any drug treatment (biopsy prior to treatment)
- Specialist biopsy again in 5-10 years if considered appropriate as part of routine care
- HCC treatment with liver resection or transplant or palliative care

Emergent project issues may result in improvement of the steps in patient recruitment and monitoring which will be documented for GP guidance as the project is implemented: please refer to the current Master Information and Consent for Participants document when informing patients of the study.

DIAGRAM 1. Hepatitis B Screening and Monitoring Overview

Patients will be stratified into management categories according to viral load and liver function identified in the Clinical Protocol
6.0 Data collection, Source Documents and Record Retention

6.1 Data collection

Every GP in the Division will be offered the opportunity to participate in the Project-related educational activities and to access the program, by recruiting their patients diagnosed as CHB or with CHB-related disease. The GP is responsible for ensuring that the data collected is complete, accurate and recorded in a timely manner.

Data will be collected using a study-specific case record form (CRF), accessible in paper and electronic format, which will capture data from the patient at first visit as a baseline (Attachment 4) and at regular follow-up visits (Attachment 5). The data is entered to the Registry database electronically from the CRF with pathology results input by download from the pathology service provider. Manual data entry from a hardcopy case-record form to the Register can be used for data collected by GPs not able to use an electronic process. Source CRF data will be stored securely by the Database Manager.

Following patient consult, the medical practitioner will submit the electronic CRF or fax or post the hardcopy CRF to the Registry central coordinating centre (Cancer Council NSW has a coordinating role, with oversight of a Database Manager operating from Westmead Hospital). The data from forms will be entered on the database and reviewed for completeness and accuracy by the Coordinating Investigator or authorised delegate (e.g., CCNSW Project Officer). Any data or process issues will be notified to the originating site investigator for clarification or action.

Where the study will be conducted in tertiary centres (Hospital Clinic sites) the CCNSW and those institutions, via the Principal investigators at that site, will permit trial-related monitoring, audits, ethics committee review and regulatory inspection providing direct access to the source documents.

Pathology data on study patients will be collected directly from the pathology service provider for prospectively recruited patients (after appropriate informed consent is obtained: refer Section 5 above).

For data exported from the Registry it is proposed that the Registry (operated by Westmead Hospital under the control of a clinical PI and a local Database Administrator) identify patients by a unique Study Participant Number (SPN) assigned by the Registry Database Manager, comprised of a 2x2 patient name code (i.e., first 2 letters of surname and first name), with an automatically generated 4 digit number assigned on enrollment. The Registry will use the Study Participant Number to identify each patient enrolled in correspondence with GPs and Specialists as needed, including notices for presentation to clinics, documentation of patient test results, treatments and outcomes. This SPN will also be used to identify patients who may otherwise be lost to follow up and on withdrawal from the project. Thus, "identified" patient information is ONLY required for longitudinal patient follow-up by the GP or Specialist in accordance with their normal clinical care and practices. Data analysis will ONLY require de-identified patient information.
6.2 Source data

The investigator should also complete accurate source documentation to support the data collected on the case record form (CRF). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Source documents include, but are not limited to, the patient medical records, laboratory reports, ECG tracings, x-rays, radiologist reports, patient diaries, biopsy reports, ultrasound photographs, patient progress notes, pharmacy records and any other similar reports or records of procedures performed in accordance with the protocol.

It is not acceptable for the CRF to be the only record of the patient participation in the study and patient progress should also be recorded in the patient medical records. This will also ensure that any one who would access the patient medical records has adequate knowledge that the patient is participating in a clinical trial.

Any document that acts as a source document (the point of the initial recording of a piece of data) should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Persons signing the source documents should be listed as a site staff member.

The sponsor and investigators agree by signature of this protocol that the investigator(s) / institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.3 Record retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice guideline. These should be organized in a comprehensive filing system that is accessible to study monitors and other relevant personnel.

The Chief Investigator must retain all study documents following completion of the study for a period of at least 15 years (i.e., this is the responsibility of CCNSW as the Sponsor). The original hardcopy documents of consent, any documents having patient identifying information or information of a confidential nature will be secured in a locked cabinet under the control of the Medical & Scientific Unit within the CCNSW. Where created within the Project, electronic files will be secured by access password authority in dedicated ‘B Positive’ Project folders within the CCNSW server system.

The Principal Investigators and Associate Investigators are responsible for ensuring that clinical records of individual patients are not accidentally destroyed and are retained in accordance with all relevant legislation, regulations and policies applying to clinical records in normal practice. Where appropriate, the relevant NSW Health policies are to be adhered to (e.g., General Retention and Disposal Authority regarding Public Health Services: Patient/Client Records (GDA 17, internal reference [40]) http://www.records.nsw.gov.au/recordkeeping/docs/gda17.pdf where “Retention periods should be in accordance with the minimum retention required for the type/s of specimens recorded in the register, see 4.3.1, and, where these records contain the details of the disposal of individual specimens, the records should be retained for as long as they might conceivably be required for the purposes of accounting for the disposal of the specimen.”)
7.0 Ethics Committee/Regulatory Approval and Informed Consent

7.1 Ethics

The Coordinating Investigator is responsible for obtaining formal Ethics Committee approval of the protocol and support documentation in compliance with the National Ethics Application Form (NEAF) process. This includes compliance with CCNSW and NSW Health requirements for a Multi-centre research application** and ensuring any local regulatory requirements are met prior to entering any patient into the study.

Cancer Council NSW Ethics Committee role**

In compliance with Cancer Council NSW Ethics Committee Standard Operating Procedures, SOP2, the Committee will review multicentre projects that involve research proposals involving the Cancer Council NSW where the project is being replicated at a number of sites or the entire project/design involves a number of sites.

1. The Committee will review multicentre projects that involve either:
   (a) Access to identifiable or potentially identifiable data owned by the Cancer Council NSW for research or other purposes; or
   (b) Linkage of data obtained from different sources within the Cancer Council NSW or the linkage of data from the Cancer Council NSW data collection with data from an external collection, or
   (c) Research proposals involving the Cancer Council NSW where the project is being replicated at a number of sites or the entire project/design involves a number of sites.

2. For projects that fall under the above categories at point 1 above, the Committee’s jurisdiction is with regard to access and linkage of Cancer Council data, and its subsequent use. The components of a project that involve access to data at the Area Health Service level or other organisations, for example hospital databases and locally held medical records, will also require review and approval by the relevant local ethics committee.

Application for decision by Sydney South West Area Health Service via the Royal Prince Alfred Hospital Human Research Ethics Committee (HREC) will be made for this multi-centre research application to cover NSW Health sites at Liverpool Hospital and Bankstown Hospitals, with approval of this single ethical review to also extend to Westmead Hospital under the Research Governance of the Sydney West Area Health Service HREC.

To ensure that all ethical issues are considered in regard to the General Practitioners and their patients involved in this project, the study documentation has also been reviewed by the Royal Australian College of General Practitioners (RACGP). The RACGP National Research and Evaluation Ethics Committee may be contacted by any person with concerns or complaints about the conduct of this study in General Practice.

Executive Officer
RACGP National Research and Evaluation Ethics Committee
1 Palmerston Crescent
South Melbourne, 3205
Email: ethics@racgp.org.au; Ph: 03 8699 0481
7.2 Informed Consent

As part of each consent discussion, investigators have an ethical and legal obligation to assess the subject's understanding of the consent information to ensure that the consent is truly "informed." When the investigator and subject do not share a language, the investigator must depend on the accuracy of the translated consent documents and the working relationship with an interpreter. It is the investigator's responsibility to judge the subject's comprehension of the consent information including the understanding that participation is voluntary and that the subject has the right to withdraw at any time during the study.

Consent must be documented by the patient's dated signature on a Consent Form (Attachment 3) along with the dated signature of the person conducting the consent discussion. If the subject is legally incompetent (i.e. mentally incapacitated) the written consent of a parent, guardian or legal representative of the patient must be obtained, however the exclusion or enrollment of such patients should be carefully considered by the clinician responsible for the provision of care as appropriately in the best interests of the patient.

If the patient is illiterate, an impartial witness should be present during the entire consent discussion. Once the discussion is complete, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the person who conducted the consent discussion.

A copy of the signed and dated consent form should be given to the patient before participation in the trial. The patient or legally accepted representative should be informed in a timely manner of any new information that becomes available during the course of the study that may affect the patient's willingness to continue participation in the trial.

Those patients meeting the selection criteria will be offered enrollment with informed consent forms collected by the clinician (GP) or Principal Investigator (if a hospital clinic recruitment), a copy retained for the investigators local records and the original forwarded to the CCNSW Coordinating Investigator for Registration. A copy of any withdrawal of consent is to be kept at the source site, and the original forwarded to the Coordinating Investigator for CCNSW record keeping.

Procedures for the Consent (Method)
1. The recruiting clinician or investigator selects a consent form in the appropriate translation for the potential participant (English, Chinese, Vietnamese form or 'oral' consent process).
2. The recruiting clinician or investigator consents an English speaking subject using the approved English consent document OR consents non-English speaking subjects using the translated form and approved English consent document.
3. The subject will read the short form consent in his/her chosen language OR an interpreter will orally translate the version of the consent document and will facilitate the question and answer phase of the informed consent process between the potential participant and the recruiting clinician or investigator.
4. A witness (who may be the interpreter) will be present during the oral presentation of the approved consent document. Note: The witness must be an adult, fluent in both languages, who is not a member of the study team (i.e., is not listed in the protocol).
5. The following signatures will be obtained on the translated form consent and the English version of the approved consent:
   a. The subject will sign and date the short form consent; and
   b. The witness and recruiting clinician/investigator will sign and date both the translated consent form consent and the English informed consent document.
6. A copy of the informed consent document will be given to the participant (for practical purposes the document may be in English and a translated language).

SUPPORTING TEXT to be considered by clinicians in using the Patient Information Statement & Protocol

It is anticipated that there will be a large number of members of the target population whose first language is Chinese, Vietnamese or another language, and who may have limited understanding of English. It is hoped that the inclusion of the NSW Multicultural Health Communication Service in the materials preparation process will facilitate cross-cultural understanding of the project, and that the GP may also be able to assist in close consultation with individual patients, family, and community leaders.

If language is an issue and none of these processes address an individuals needs appropriately, the GP/Specialist or Project staff undertaking the recruitment will arrange for an appropriate translator to accompany them for interview. (This was included in the answer to NEAF Ethics Form question Section 6.1)

If a person has literacy problems and is not able to read, in obtaining consent for information to be included on the record (Drs notes, database etc), the provider will need to read to them the information proposed to be included in the ‘B Positive’ Project Patient Information Sheet and Consent Form, rather than simply show a printout to them. The details of these arrangements need to be developed and cleared with the Division of General Practice and key individual recruiting clinicians who will be provided a clear procedural guideline as part of their participation in this project.


IMPORTANT NOTE: It is the investigator's responsibility to judge the subject's comprehension of the consent information including the understanding that participation is voluntary and that the subject has the right to withdraw at any time during the study. If the investigator doubts the subject's consent comprehension, he/she should not enroll the subject in the study. The subject's autonomy must not be jeopardized due to a language barrier. (Source: http://www.rgs.uci.edu/ora/rp/hrpp/non-englishspeakingparticipants.html#Informed)

** refer EthicsCommittee_CCNSW_OperatingProcedures_Jan2007 requirements for multi-centre application

8.0 Confidentiality of data

8.1 Confidentiality of patient records

By signing of the protocol, the investigator agrees that the study co-coordinators or their representative, ethics committee or regulatory authorities may consult and/or copy
study documents to verify information in the Chronic Hepatitis B Project Registry database. By signing of the consent form the patient agrees to this process.

Patient confidentiality will be maintained at all times. If study documents need to be photocopied during the process of verifying case record form data, the patient will be identified by a unique code only; full names and other identifying information will be masked, unless such masking would invalidate the process (e.g., verifying CRF data held in the database against a suspected error such as duplicate data entry requires full detail).

A statement of how the confidentiality of patient records will be protected will be included in the “Patient Information Sheet” (Attachment 3) which is to be provided as part of obtaining their consent. (i.e., any identifiable information that is collected about patients in connection with this study will remain confidential and will be disclosed only with written permission, or except as required by law. Only the researchers named above or those persons responsible for delivering clinical care in the course of a patient’s normal management at a participating practice or healthcare facility will have access to these details and results that will be held securely at such facilities or within the Registry database that is hosted by the Westmead Hospital, Sydney [institution]).

8.2 Confidentiality of study data

By signing this protocol, the investigator affirms to the sponsor that information provided to the investigator by the sponsor will be maintained in confidence and will be divulged only as necessary to the ethics committee and institution employees directly involved in the study.

The data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as agreed in the publication policy of this protocol.

The sponsor (CCNSW) and investigators agree by signature of this protocol that the investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

The “Patient Information Sheet” (Attachment 3) provides a full explanation of how and where information collected from participants will be stored while the project is being conducted and after it has been completed.

Confidentiality will be protected by reporting aggregated results where possible. Where appropriate, using pseudonyms for individual participants or locations in this project will be reported where the reporting of such results maintains confidentiality (e.g., patient case-study example or comparison of geographic or site of service locations).

9.0 Financing and Insurance

The study Sponsor (CCNSW) is the principal funding body of this study, employing project staff, consultants, engaging volunteers or committing other resources in accordance with its corporate policies as part of its normal business activities.

No payment by CCNSW to Principal or Associate Investigators is agreed for their participation in this study.
‘B Positive’ Project

GPs may be eligible for payment under the Medicare Benefits Schedule (MBS) for Enhanced Primary Care (EPC) Care Planning payments in respect to CHRONIC DISEASE MANAGEMENT ITEMS (Items 721 to 731) which are applicable to their management of the CHB patient. These items provide rebates for GPs to manage chronic disease by preparing, coordinating, reviewing or contributing to CDM plans, however such MBS claims are not part of the study funding and payment is subject entirely to MBS normal requirements (for details refer to MBS Online http://www9.health.gov.au/mbs/fullDisplay.cfm?type=note&q=A.28&qt=noteID&criteria=chronic%20disease).

Given the arms-length relationship between the Sponsor and the care provided by any clinician to patients enrolled in the study, there is no insurance agreement or waiver of liability expressly given or implied by the Investigators or the Sponsor to each other.

Normal ‘duty of care’ and other obligations to participants are expected to apply for all clinical care and other, including administrative, support delivered by individual investigators, institutions or commercial entities. The Sponsor has no specific risk-related insurance coverage for patients, investigators or other external (non-CCNSW parties) associated with the study.

Additional information (in all forms as documents, www resources, or other forms) is to be provided by the medical practitioner to an individual with consideration of their individual Duty of Care to that patient/ carer and does not imply such additional information is endorsed by the Cancer Council NSW, the Project Steering Committee members, or any other party as appropriate for use in the individuals circumstances.

10.0 Publication Policy

The investigators agree (by signing the Clinical Protocol) to a Publications Policy which identifies the PROCESS for authors and acknowledgement of the research team. Concept sheets or an abstract of the proposed publication, including details of authorship for any sub-studies/analyses or publications arising from this study, must be submitted to the Coordinating Investigator for Project Steering Committee approval prior to presentation or submission of an abstract for publication.

By signature of this Protocol the Investigators agree that any publication arising from this study will be at least attributed to the principal authors of the publication (for example, in accordance with established University academic policies). In addition, on all publications the collaborative efforts of the parties to this study will be formally acknowledged in the publication (i.e., in the author listing or an Acknowledgement section) with the additional words: On behalf of the Cancer Council NSW ‘B Positive’ Project investigators.

ATTACHMENTS*

1. Protocol Appendix 1. Screening program test protocol flowchart
2. Protocol Appendix 2. Screening & monitoring program flowchart
3. Participant information sheet and consent form
4. Case Record Form (Baseline) &
5. Case record Form (Follow-Up visits)

* Note: This Protocol has been reviewed by a Lead Human Research Ethics Committee (SSWAHS (RPAH Zone) under the National Ethics Application Form process. An Investigator’s Pack may comprise the above Clinical Protocol and Attachments, with additional general and project-specific information if appropriate, from a variety of sources (e.g., NSW Health and CCNSW information for patients/ carers). Such resources are not part of the Protocol.
References


**Glossary Of Abbreviations**

| Ab | Antibody |
| AE | Adverse event |
| AFP | Alpha-1-fetoprotein |
| Ag | Antigen |
| ALT (SGPT) | Alanine aminotransferase (liver function test) |
| α1 AT | Alpha 1 antitrypsin |
| AMA | Anti-mitochondrial antibodies |
| ANA | Anti-nuclear antibodies |
| ANOVA | Analysis of variance |
| AP | Alkaline phosphatase |
| AST(SGOT) | Aspartate aminotransferase |
| AUC | Area under the plasma concentration-time curve |
| b.i.d. | Twice daily |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CHB | Chronic hepatitis B |
| CHC | Chronic hepatitis C |
| CI | Confidence interval |
| Cmax | Maximum plasma concentration |
| CMV | Cytomegalovirus |
| CRF | Case Record (or Report) Form/s |
‘B Positive’ Project

CTL         Cytotoxic T-Lymphocyte
CXR         Chest x-ray
DMT         Drug Maintenance Therapy
DNA         Deoxyribonucleic acid
ECG         Electrocardiogram
ESF         Eligibility screening form
GGT         Gamma glutamyl transferase (liver function test)
h           Hours
HAV         Hepatitis A virus
HBc         Hepatitis B core
HBsAg       Hepatitis B surface antigen
HBeAg       Hepatitis B virus ‘e’ antigen
HBV         Hepatitis B virus
HCC         Hepatocellular carcinoma
HCV         Hepatitis C virus
HIV         Human immunodeficiency virus
ICH         International Conference on Harmonization
IEC         Independent (Institutional) Ethics Committee
IDU         Injecting drug user
IEC         Independent Ethics Committee
IFN         Interferon alpha
IRB         Institutional Review Board
IgM         Immunoglobulin M antibody
ITT         Intention to treat
iv          Intravenous
LFT         Liver function test (see also ALT and GGT)
μg          Microgram
mg          Milligram
mL          Milliliter
MIU         Million International Units
mRNA        Messenger ribonucleic acid
ng          Nanogram
PCR         Polymerase chain reaction
PD          Pharmacodynamic
PE          Pharmacoeconomic
PEG-IFN     Pegylated-Interferon alfa-2a
PK          Pharmacokinetic
po          per os
RBV         Ribavirin
PR          Pulse rate
QoL         Quality of life
RIA         Radio immunoassay
RNA         Ribonucleic acid
RBC         Red blood count
SAE         Serious adverse event
sc          Subcutaneous
SI          System International
SRB         Safety Review Board
t.b.d.      To be determined
tiw         Three times per week
ULN         Upper limit of normal
US          Ultrasound
WBC         White blood count