The feasibility of screening for viral hepatitis in immigrant populations

Dr Victoria Jayne Appleby MBChB, MRCP

Submitted in partial fulfilment of the requirements of the Degree of Doctor of Medicine by Research

Statement of originality

I, Victoria Jayne Appleby, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis.

I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

Signature:

Date:22/06/2017

Abstract

Globally, it is estimated that 240 million people are infected with chronic viral hepatitis B and in excess of 185 million people with chronic hepatitis C. The burden of disease from hepatitis is concentrated in developing countries where transmission of HBV occurs predominantly from mother to child (vertical transmission) and transmission of HCV through unsafe medical procedures and the transfusion of unscreened blood products.

Global patterns of migration favour the movement of individuals from countries with medium or high risk prevalence of chronic viral hepatitis to countries with traditionally low prevalence among their indigenous populations, including the United Kingdom (UK). In excess of 3.2% of the global population are international migrants, posing important implications for healthcare systems in host nations. It is predicted that up to 7 million first and second generation immigrants, originating from high prevalence countries for viral hepatitis now reside permanently in the UK. However, as a result of deficiencies in screening initiatives, the prevalence and associated burden of these diseases in these high-risk populations residing in the UK is yet to be determined.

In order to establish the feasibility of inviting first and second generation immigrant populations to participate in viral hepatitis testing in primary care, as well to determine the prevalence and demography of viral hepatitis in four areas of the UK, a randomised controlled cross sectional cluster trial was conducted. In HepFree clinical computer systems in general practice surgeries were interrogated to identify the target population that was then approached using a variety of different invitations to determine the most appropriate method for engaging this population.

The outcomes of viral hepatitis testing from practices in one area of the UK are described in this thesis. Despite multiple challenges encountered both in engaging practices and individuals in trial participation, results of this investigation suggest that if it is found to be cost effective, then viral hepatitis screening is feasible and the burden of disease in the UK is concentrated in first generation immigrants.

Table of Contents

List of Figures

List of Tables

List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ALT	Alanine transaminase
Anti-HBe	Anti-hepatitis B e antigen
Anti-HCV	Antibodies to hepatitis C
BBV	Blood-borne virus
BMI	Body mass index
APASL	Asian Pacific Association for the Study of the Liver
cccDNA	Covalently closed circular deoxyribonucleic acid molecule
CCL-3	Chemokine ligand 3
CCG	Clinical commissioning group
CD4+	Cluster of differentiation 4 positive T-cell
CD8+	Cluster of differentiation 8 positive T-cell
CD-28	Cluster of differentiation 28
CDC	Centers for Disease Control
CI	Chief Investigator
CMIA	Chemoiluminescent microparticle immunoassay
CNS	Clinical nurse specialist
CTLA-4	Cytotoxic T-lymphocyte associated antigen 4
CV	Curriculum vitae
CYP3A	Cytochrome P450 3A
DAA	Direct-acting antiviral
DBS	Dry blood spot
DNA	Deoxyribonucleic acid
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
E1	Envelope-1 glycoprotein
E2	Envelope-2 glycoprotein
EASL	European Association for the Study of the Liver
eCRF	Electronic case report form
email	Electronic mail
eRVR	Extended rapid virological response
EAP	Early access programme
ER	Endoplasmic reticulum
ETR	End of treatment response
EVR	Early virological response
FCH	Fibrosing cholestatic hepatitis

GDBS	Global database on blood safety
GP	General practice
GUM	Genito-urinary medicine
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HE	Hepatic encephalopathy
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HRQL	Health related quality of life
ID	Identifier
IFN	Interferon
IHD	Ischaemic heart disease
IL-2	Interleukin 2
IRAS	Integrated Research Application System
IT	Information technology
ITT	Intention to treat
IVDU	Intravenous drug use
LFTs	Liver function tests
MELD	Model of End-Stage Liver Disease
MHE	Minimal hepatic encephalopathy
MRS	Magnetic resonance spectroscopy
MSK	Musculoskeletal
NA	Nucleoside anologue
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health and Research
No.	Number
NPI	Nucleotide polymerase inhibitor
NNPI	Non-nucleotide polymerase inhibitor
NR	Null response
NS	Non-structural
NS3	Non-structural 3 protein

NS4B	Non-structural 4B protein
NS5A	Non-structural 5A protein
OLTx	Orthotopic liver transplant
OR	Odds ratio
PBC	Primary biliary cirrhosis
PCR	Polymerase chain reaction
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
Peg-IFN	Pegylated interferon
PI	Principal Investigator
PIs	Protease inhibitors
PIS	Patient information sheet
POCTs	Point of care tests
PR	Partial response
PWID	People who inject drugs
QOF	Quality and Outcomes Framework
QOL	Quality of life
R&D	Research and development
rcDNA	Relaxed circular hepatitis B virus deoxyribonucleic acid
RCGP	Royal College of General Practitioners
RER	Rough endoplasmic reticulum
RNA	Ribonucleic acid
RVR	Rapid Virologic Response
S1	SystmOne
sd	Standard deviation
SF-36	Short Form 36
SIV	Site initiation visit
SVR	Sustained virological response
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TE	Treatment experienced
Th-1	Type 1 T-helper
Tim-3	T-cell immunoglobulin and mucin-domain containing-3
TN	Treatment naïve
TNF	Tumour necrosis factor
ULN	Upper limit of normal
UK	United Kingdom

UN	United Nations
VL	Viral load
WHO	World Health Organisation

List of units and symbols

IU/mL	International Units per Millilitre
IU/L	International Units per Litre
α	Alpha
ɣ	Gamma
>	More than
<	Less than

1. Introduction

1.1 Overview

Globally, it is predicted that in excess of 400 million people are infected with chronic viral hepatitis B and C (HBV, HCV) (1,2). The burden of disease associated with viral hepatitis is concentrated in developing countries where transmission of HBV is most often vertical, from mother to child, and transmission of HCV is from unsafe medical procedures and the transfusion of unscreened blood products. In developed countries including the United Kingdom (UK), the majority of cases of viral hepatitis arise as a result of injecting drug use. Multiple initiatives have been developed and implemented in this group of high-risk individuals to improve testing, diagnosis, and treatment of viral hepatitis.

In England, HBV and HCV prevalence is estimated to be 0.5 and 1% respectively (3,4). There is uncertainty surrounding the validity of these data for the following reasons; the unknown prevalence of disease in developing countries, the patterns of migration from high-risk to low-risk countries and the absence of formal screening programmes for viral hepatitis in non-indigenous populations residing in England.

Global patterns of migration favour the movement of individuals from countries with medium or high-risk prevalence of chronic viral hepatitis to countries with traditionally low prevalence among their indigenous populations, one of which includes the UK. In 2015, the United Nations (UN) estimated that 3.3% of the global population were international migrants, posing important implications for healthcare systems in host nations (5). It is predicted that up to 7 million first and second generation immigrants originating from high prevalence countries now reside permanently in the UK and this figure is likely to be a conservative estimate of the true volume of migration (6). Previous studies conducted in migrant populations in developed countries have suggested that the prevalence of disease in these groups reflects the disease prevalence in their country of origin (7,8).

Chronic infection with viral hepatitis, in particular HCV, causes progressive damage to the liver resulting in cirrhosis, with or without the development of hepatocellular carcinoma (HCC). Highly effective antiviral therapies are available for the treatment of both HCV and HBV. Sustained virological response (SVR) otherwise known as ‘cure’ rates exceed ninety percent in individuals with genotype 1 HCV infection treated with new regimens (9,10) and up to eighty percent in individuals with genotypes 2 and 3 infection (11). Despite the availability of these highly effective treatments, research has highlighted that identification of high-risk groups,

detection and subsequent treatment of viral hepatitis in the UK has previously been and continues to be suboptimal (12).

The development of these highly effective antiviral therapies has, for the first time, made elimination of HCV a possibility. The term elimination refers to a reduction to zero in the incidence of new infections caused by HCV in a defined geographical area. This reduction in incidence occurs as a result of deliberate efforts made and requires continued action to prevent re-establishment of transmission of the virus. In HCV, the deliberate efforts include the development and implementation of highly rigorous and effective case-finding programmes that target 'at risk' populations as well as promoting engagement with treatment and probably, most importantly, prevention education. Whilst future elimination of HCV is a possibility, eradication may not be. The term eradication refers to the complete and permanent world-wide reduction of a disease to zero cases without the need for further intervention or disease control measures. Although HCV has a limited host range and there are highly effective DAAs available for the treatment, the absence of a pan-genotypic vaccine, poor linkage to care for individuals diagnosed with the disease, the high current high cost of HCV treatment, and the potential risk of re-infection due to an un-diagnosed reservoir of infection in 'difficult to reach' populations are all factors that will prevent HCV eradication.

HepFree, a randomised controlled cross-sectional cluster trial aimed to assess the feasibility and cost-effectiveness of case identification and subsequent treatment of viral hepatitis in immigrants originating from countries with a known prevalence of viral hepatitis of more than two percent. The trial was developed by Professor Graham Foster, and following successful application, was funded by the National Institute for Health and Research (NIHR) through the Programme Grants for Applied Research.

The trial performed targeted testing for viral hepatitis in immigrants in General Practices (GP) in four geographically distinct areas of England. Potential study participants were identified from lists of registered patients stored on clinical computer systems within practices. Participants were identified from pre-existing demographic data that was documented within their individual electronic medical record. Once identified, potential study participants were sent an invitation through the post to attend for a viral hepatitis screening test. HepFree commenced screening in Bradford, East London and South London in March 2014 and later in Oxfordshire in August 2015.

Through performing targeted testing in high-risk immigrant populations, we aimed to establish the demography of viral hepatitis in these groups of individuals in certain geographic locations in England. Specific outcomes included disease prevalence, the characteristics of individuals affected and the associated burden of disease. In addition to determining the prevalence of disease, through its methodology, HepFree aimed to establish the most effective way of engaging this population; letter invitation versus opportunistic testing. Finally by offering treatment to trial participants with a diagnosis of viral hepatitis in a variety of locations; satellite viral hepatitis clinics in the community outside of secondary care in addition to in secondary care (standard of care) the trial examined the impact of different locations on engagement, compliance and adherence to treatment.

As the clinical fellow employed to work on the HepFree trial in Bradford, once full sponsorship for the trial had been granted in London, my first role was to set up Bradford as a coordinating trial site. In order to do this, I facilitated the development and implementation of a contract between Barts Health NHS Trust and Bradford Teaching Hospitals NHS Foundation Trust. Once the contract had been finalised, site feasibility was completed and an agreement produced between the Research Development team at Bradford Teaching Hospitals and the Research Management Group at the Bradford District Care NHS Foundation Trust to enable the trial to be performed in GP surgeries in the community. Prior to recruiting practices to act as trial sites, I designed and created the searches that would be used on the clinical computer systems in primary care to identify potential study participants. These searches were designed to identify individuals registered at each practice that originated from countries with a prevalence of viral hepatitis of more than two percent. The searches identified potential study participants based on Read codes relating to ethnicity, country of birth and main spoken language that were recorded within each electronic medical record. The searches are described fully in Materials and Methods. Once the searches had been developed and tested, recruiting practices that would perform the hepatitis testing commenced.

In Bradford, I was solely responsible for recruiting, initiating, opening and assisting in the running of the trial in twenty-one practices. Once sites had opened and targeted testing had commenced, all participants with a positive hepatitis test were offered an appointment to attend a diagnostic assessment appointment in secondary care. I was responsible for the assessment, management and follow-up of all participants with a positive test. Depending on

the outcome of randomisation, following the diagnostic assessment, subsequent appointments for treatment either took place in secondary care or in a satellite viral hepatitis clinic based at a GP surgery in the community. In addition to these roles, I also collected, collated and entered all trial related data into trial electronic case report forms (eCRF). In conjunction with the clinical fellow and data manager in London I had assisted in the development of, and testing of the aforementioned eCRF. In Bradford, all clinical duties were overseen locally by the principal investigator (PI) and centrally by the trial chief investigator (CI).

In addition to my roles in the national HepFree study, I designed, developed and implemented a unique sub-study exploring symptoms and healthcare utilisation in individuals with undiagnosed chronic HCV that had been identified through the HepFree trial. The full methodology of the HepFree trial and the retrospective case-control sub-study are discussed in Materials and methods.

1.2 The Hepatropic viruses

Worldwide, the vast majority of cases of viral hepatitis are caused by hepatitis viruses A, B, C, D and E. The natural history, routes of transmission, clinical manifestations, long-term consequences, and options for immunisation vary significantly between the viruses. This thesis concentrates on hepatitis B and C viruses, however hepatitis A, D and E will be discussed initially.

1.2.1 Hepatitis A

Hepatitis A (HAV) is a single stranded, non-enveloped RNA virus belonging to the picornavirus family. Transmission is predominantly faecal-oral, and presents clinically as an acute hepatitis with deranged liver function tests (LFTs) and jaundice. Advancements in public health sanitation and an improvement in overall standards of living as well as the development of a vaccine have resulted in a decrease in the worldwide incidence of acute HAV infection (13). Mortality secondary to HAV, as a result of fulminant hepatic failure is rare, the estimated annual mortality rate is 1.2 deaths per 1 million persons (14). Infection with HAV does not progress to chronic liver disease (15).

1.2.2 Hepatitis D

Hepatitis D virus (HDV) is a defective RNA virus, dependent on HBV for its lifecycle (16). The delta virus shares envelope proteins from HBV to enable attachment and entry into host cells (17–19). Infection with HDV can occur simultaneously with HBV, known as co-infection, or subsequently, termed as super-infection (20). Infection with HDV causes severe liver disease with rapid progression to cirrhosis (21–25). Areas of endemicity include central and the horn of Africa, the Amazon basin, Eastern and Mediterranean Europe as well as the Middle East and parts of Asia (26). It is estimated that in excess of 15 million people with chronic HBV infection have been exposed to and infected with HDV, corresponding to a global prevalence of approximately five percent (20). In prevalence studies conducted in European countries including Italy, a decline in infection rates with HDV have been observed. Investigators summarised that this change in prevalence has occurred in response to a decline in the prevalence of new HBV infections as a result of increased awareness, education and the development of a vaccine (27,28). This decrease in prevalence however was not observed when the authors examined a further cohort of Italian subjects with chronic HBV in 2006, where a slight increase in prevalence was seen, nor has it been observed in other European countries including the UK, where a rise in new cases of infection have been attributed to immigration (29–31).

The current treatment option available for HDV infection is pegylated interferon alpha (32). Studies investigating the efficacy of interferon have demonstrated HDV negative rates of approximately 15-40% in individuals followed up twenty-four weeks after stopping therapy (33–35).

1.2.3 Hepatitis E

Hepatitis E virus (HEV) is a positive-sense, single stranded RNA virus, transmitted predominantly via the faecal-oral route (36). Similarly to HAV, the highest rates of infection are observed in areas of the world with poor standards of sanitation. Acute infection results in a mild, self-limiting illness except in the context of pregnancy when infection can result in fulminant hepatitis with an associated mortality of up to thirty percent (37,38). In addition to the increased risks associated with infection during pregnancy, a small case series performed in France identified that acute infection with HEV in organ transplant recipients can result in

chronic infection with progressive development of fibrosis (39). Annually there are approximately 20 million episodes of infection with 3.3 million symptomatic cases of HEV and approximately 56,600 deaths (40).

1.3 Hepatitis B

Hepatitis B is a partially double-stranded, enveloped DNA virus belonging to the hepadnaviridae family (41). Infection can either be acute or chronic, and clinical outcomes for both are discussed within this section. Acute infection with HBV is either sub-clinical, or can be associated with constitutional symptoms including loss of appetite, muscle aches, malaise, fatigue and occasionally a fever. Diagnosis is made with serum; the first marker detected in the blood of acutely infected individuals is HBV DNA, followed by hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), the presence of which indicates high viral replication (41). Acute infection is accompanied by elevated liver enzymes and complicated by jaundice in approximately ten percent of young children and in up to thirty to fifty percent of adults infected (41). In contrast to cases of acute infection, chronic infection with HBV is predominantly asymptomatic with symptoms arising only as a result of progression to chronic liver disease.

The modes and patterns of transmission of HBV vary depending on the country and population sub-group studied (42). Infection with HBV can occur through the following routes: vertical transmission in the perinatal period, horizontal transmission between household contacts, unprotected sexual intercourse, intravenous drug use (IVDU) and either percutaneous or parenteral contact with infected blood (43). In countries with high endemicity including Africa and Asia, infection predominantly occurs in the perinatal period (43,44). Conversely, in low endemic countries, sexual intercourse is the predominant mode of transmission with the risk of infection increased in the following groups; men who have sex with men, individuals with multiple sexual partners and individuals with co-existing sexually transmitted infections (43).

Chronic HBV is defined as persistence of the virus for more than six months after initial infection and is diagnosed by the presence of HBsAg in blood. Chronic infection represents a global health problem. Worldwide there are estimated to be in excess of 240 million cases of chronic HBV infection and annually 1.2 million deaths are attributed to complications of chronic hepatitis including cirrhosis and HCC (43). Long-term infection can lead to cirrhosis of the liver and the development of HCC which can occur in the absence of hepatic cirrhosis (45). The rate of spontaneous viral elimination in individuals with chronic infection is approximately one to two percent per annum (46). Viral and host factors associated with HBsAg clearance include advancing age (47,48), the presence of moderate to severe hepatic

steatosis (49), genotype A infection (50) and anti-HBe positive status in combination with low serum surface antigen and low HBV DNA levels (51–53).

Host age at the time of infection has a significant impact on the clinical course of the HBV. Viral infection in adulthood is associated with a ninety-five percent chance of clearance, whereas infection occurring during infancy results in chronic infection in approximately ninety percent of cases (54). Vaccination is the single most effective method of preventing individuals from contracting HBV infection. Historically, targeted vaccination in high risk populations was recommended however due to difficulties in identifying and engaging these populations, this method is seldom superior to universal vaccination. The World Health Organisation therefore recommended that HBV vaccination be incorporated into the Expanded Program on Immunisation and following this, a significant decrease in chronic HBV infections was observed. A minority of European countries including the UK are yet to adopt universal screening policies and therefore transmission here still poses as a much greater threat.

1.3.1 The natural history of HBV

Historically, chronic HBV acquired during childhood consisted of four phases of infection; immune tolerance, immune clearance, the inactive carrier state and HBV reactivation otherwise known as HBeAg negative chronic hepatitis (55,56). Individuals infected with HBV can move back and forth between these four phases of infection.

Within this section I will discuss the well-documented phases in the natural history of HBV in addition to more contemporary research that has challenged some of the more traditional definitions.

1.3.1.1 Immune tolerance

The immune tolerant phase of HBV is defined by a high circulating viral load (VL) in combination with positive HBeAg serology, normal serum alanine transaminase (ALT) levels and little or no evidence of hepatic inflammation on histological assessment of the liver (56–58). Historically, it was hypothesised that high rates of chronic infection and the immune

tolerant phase of infection observed in infants was the result of trans-placental transfer of viral proteins coupled with HBV-specific T-cell hyporesponsiveness and an inefficient T-cell response.

The concept of immune tolerance has been challenged by authors who suggest that chronic infection in children is neither associated with an insufficient nor a tolerant T-cell profile (59). In a study by Kennedy et al, T-cell cytokine profiles obtained from young adults with chronic HBV were compared to age-matched non-infected 'healthy' subjects. In this study T-cells from infected individuals demonstrated superior ability to produce antiviral cytokines compared to healthy controls. In addition to this, an increased expression of exhaustion markers on the T-cells of young individuals with chronic HBV was observed compared to the healthy control cohort (59).

T-cell exhaustion occurs as a consequence of repetitive activation of reactive T-cells. This finding therefore contradicts the theory that infants and young adults with chronic HBV display tolerance to the virus (59). One other finding presented in this study further questioned the definition of the immune tolerant phase of infection. In both the infected and non-infected cohorts, the frequency of chemokine ligand 3 (CCL-3) producing T-cells were measured. These were lower in the 'immune tolerant' infected cohort compared to both age-matched healthy controls and individuals with chronic active disease. Elevated CCL-3 levels are found in the serum of individuals with T-cell mediated liver disease, therefore the investigators speculated that defective production of CCL-3 is responsible for the normal ALT levels that are observed and form part of the accepted definition of immune tolerance (59).

The observation of minimal or no hepatic fibrosis at the time of histological assessment also forms part of the definition of immune tolerance. This finding was supported by results from a liver biopsy trial performed in individuals with chronic HBV in China (60). In this trial, participants underwent histological assessment using liver biopsy prior to recruitment and were then followed with a period of observation and serial ALT monitoring once every six months for five years. Exclusion criteria for the trial included the presence of fibrosis, Ishak score of greater than one on liver biopsy. Participants were later withdrawn from follow-up in the event of an elevated ALT result (60). During the trial, sixteen percent of subjects were prematurely withdrawn, and repeat biopsies in all cases demonstrated progression of fibrosis. The remaining participants that completed follow-up fulfilled the definition of 'immune tolerance', with evidence of either little or no fibrosis progression during the five year period

of observation (60). The slow progression of fibrosis demonstrated in participants that remained in this study was supported by a paired transient elastography study performed in HBeAg positive individuals (61).

Contradictory results were obtained in a study conducted in individuals with HBeAg positive disease by Lai et al. Here eighteen percent of individuals with ALT values of less of less than 40 IU/L on at least two occasions in the preceding six months had evidence of histologically active disease; Ishak fibrosis stage of two or greater on liver biopsy. This study questioned the reliability of a 'normal' ALT in predicting fibrosis. Trial limitations identified by the authors were that both the age and VL of the subjects studied were not typical of those in the immune tolerant phase of infection. A liver biopsy study performed in 452 participants with chronic HBV in different phases of infection further questioned the reliability of a normal ALT in predicting fibrosis. Here, irrespective of the value of ALT, histological evidence of inflammation was present within the liver of all individuals included in the trial (62). More advanced fibrosis was observed in HBeAg negative individuals compared to HBeAg positive subjects, however, approximately five percent of individuals with HBeAg positive disease did have evidence of advanced fibrosis (62).

1.3.1.2 Immune clearance

Individuals with chronic HBV typically enter the immune clearance phase of infection between the third and fifth decades of life. This phase is defined as a period of immune-mediated liver damage manifesting as either intermittent or persistent elevations in serum ALT, combined with high HBV DNA levels and histological features of necro-inflammation with varying degrees of fibrosis on liver biopsy (58). In this phase of infection, individuals either seroconvert from HBeAg positive to HBeAg negative, anti-HBe positive disease, often associated with VL suppression, or they fail to seroconvert, resulting in persistent hepatic inflammation and the development of fibrosis (58). A well-documented relationship exists between the severity of ALT rise observed in individuals during the immune active phase of infection and the subsequent rate of seroconversion to anti-HBe positive disease (63). In a large longitudinal study of individuals of Chinese origin with chronic HBV, more than half of all participants with an ALT rise to greater than five-times the upper limit of normal (ULN) spontaneously seroconverted to anti-HBe compared with twenty-six percent of individuals with an ALT rise to less than five- times the ULN (64).

1.3.1.3 Anti-HBe positive HBV

Following seroconversion, individuals with chronic infection either progress to an inactive phase of infection characterised by minimal, if any necroinflammatory activity within the liver, or alternatively they have on-going evidence of hepatic inflammation. The following criteria are used to diagnose the inactive carrier state: HBeAg negative, anti-HBe positive serology in conjunction with normal ALT levels and a HBV DNA of equal or less than 2.0 $x10^3$IU/mL (32). Individuals may not remain in this inactive phase of infection permanently, instead progressing to a second immune active phase referred to as HBeAg negative chronic hepatitis. This is diagnosed by the presence of either transient or persistent elevations in serum ALT levels with serum HBV DNA levels exceeding 2.0 $x10^3$IU/mL (65).

1.3.2 Virology and immunology

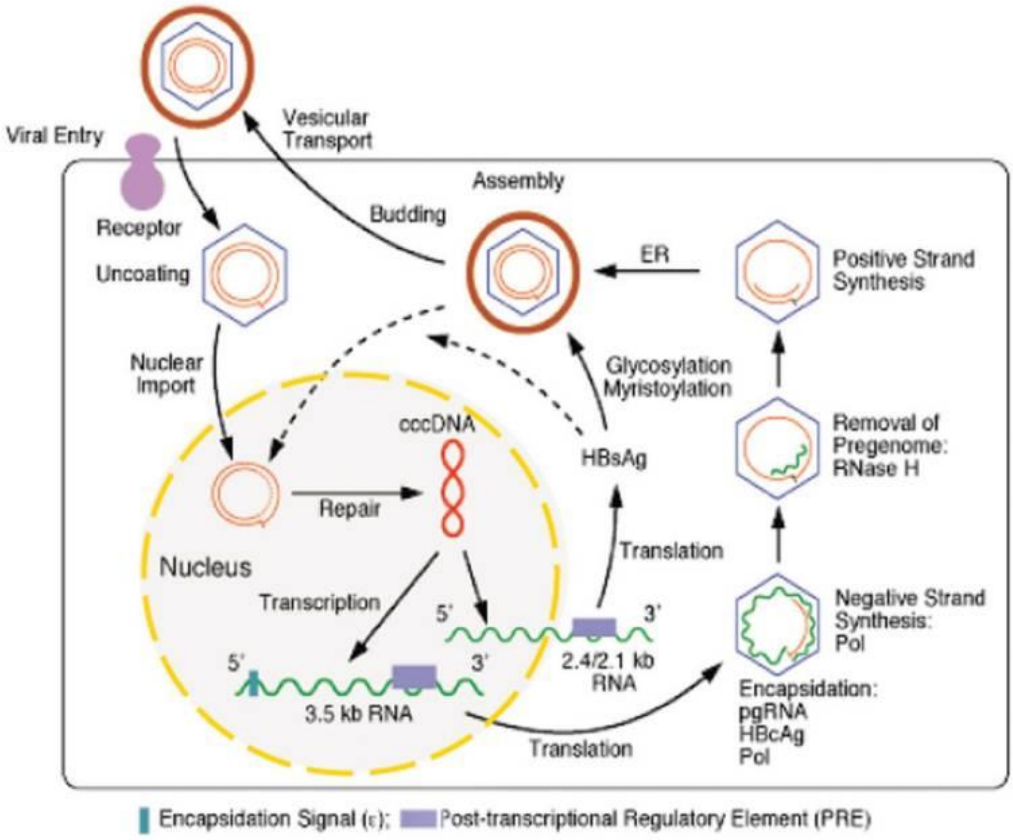
HBV is a partially double-stranded, enveloped DNA virus originating from the hepadnaviridae family (41). The infectious portion of the virus, referred to as the Dane particle, consists of an outer envelope composed of lipids and glycoproteins including HBsAg and an inner nucleocapsid, containing a copy of double-stranded HBV DNA and the HBV DNA polymerase enzyme enclosed by hepatitis B core antigen (66). Interactions between cell surface receptors and viral envelope proteins enable HBV entry into host hepatocytes. Following binding of the virus, cell entry occurs as a result of endocytosis and the nucleocapsid is released into the cell cytoplasm.

Once inside the cell, the virus nucleocapsid is uncoated and relaxed circular HBV DNA (rcDNA) is released into hepatocyte nucleus where it is repaired and converted into a covalently closed circular DNA molecule (cccDNA). This DNA molecule serves as the template for subsequent viral RNA transcription.

The double stranded HBV DNA genome encodes four major RNA templates, the largest of which has dual function acting both as messenger RNA and as pre-genomic RNA. The translation of viral RNA into HBV proteins involves four overlapping open reading frames: surface envelope (S), core (C), polymerase (P) and X protein. The S and C open reading frames possess in-frame initiation codons that facilitate the translation of different HBV proteins. Core antigen and pre-core proteins are encoded for by C and the S open reading frame encode three surface envelope proteins; small, middle and large surface antigen.

In the host cell endoplasmic reticulum (ER), pre-core proteins undergo proteolysis to become HBeAg. This is responsible for both promoting chronic infection in the host and acts as an important marker for viral replication (67). The P open reading frame encodes HBV polymerase, this has multiple roles including the synthesis of HBV DNA, reverse transcriptase which catalyses genome synthesis and the degradation of pregenomic RNA (41). The functions of HBV X antigen protein encoded by the X open reading frame include signal transduction, transcriptional activation, DNA repair and protein degradation, necessary for productive HBV infection in vivo (41). The HBV nucleocapsid is then assembled within the cytoplasm of the hepatocyte. Pre-genomic RNA is encapsidated by cytoplasmic viral proteins where it acts as a template for reverse transcriptase leading to synthesis of new HBV DNA molecules. The infective virions are then transported to the ER of the cell for further assembly and excreted from the infected cell through a process of budding and vesicular transport. Within the nucleus of the infected hepatocyte, cccDNA continues to exist and is resistant to eradication.

Figure 1: Hepatitis B virus replication



A diagram demonstrating a replication cycle of HBV as described in the text above.

Image taken from Hepatitis B: The Virus and Disease, Liang 2009.

As previously stated, acute HBV infection in adulthood is associated with high rates of viral clearance. The predominantly self-limiting nature of infection is the result of cluster of differentiation 4 positive (CD4+) and cluster of differentiation 8 positive(CD8+) T-cell responses. CD4+ T-cells target HBV-core antigen epitopes producing the Type 1 T-helper (Th-1) cytokines interferon-gamma (IFN-ɣ) and tumour necrosis factor-alpha (TNF-α). Simultaneously, CD8+ T-cells are also activated, these are the major immune cells that contribute to viral clearance (68,69). Impaired HBV-specific T-cell responses and progressive loss of T-cell function, known as T-cell exhaustion, have been identified as the reasons for viral persistence and development of chronic HBV (70).

In an exhausted state the proliferative capacity of T-cells is disrupted, cytokine production is impaired and there is up-regulation of the following inhibitory molecules; programmed cell death 1 (PD-1), cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), CD244, and T-cell immunoglobulin and mucin-domain containing-3 (Tim-3)(71,72). Increased expression of the aforementioned co-inhibitory receptors in addition to the apoptosis gene BCL2-interacting mediator BIM occur in response to high levels of HBV antigen and DNA.

Increased expression of these inhibitory molecules results in a reduction of T-cell responsiveness hindering viral elimination (71). The role of each of the HBV exhaustion markers is discussed below.

1.3.2.1 Programmed cell death-1

PD-1 is the dominant inhibitory receptor on HBV specific CD8+ T-cells. Up-regulation of PD-1 expression occurs in response to a high HBV viral load (73). A study investigating the effect of programmed death-ligand 1(PD-L1) blockade in peripheral mononuclear cells demonstrated partial improvements in both the expansion of, and cytokine secreting ability of CD8+ T-cells (73).

1.3.2.2 Cytotoxic T-lymphocyte associated antigen 4

Cluster of differentiation 28 (CD-28) dependent T-cell activation and production of interleukin-2 (IL-2) are both prevented by CTLA-4 (74). A positive correlation has been identified between HBV-specific CD8+ T-cell expression of CTLA-4 and HBV viral load (75). Blockade of CTLA-4 results in decreased expression of BIM as well as increased proliferation of IFN ɣ producing T-cells in both peripheral mononuclear cells and in hepatocytes (75,76).

1.3.2.3 T-cell immunoglobulin and mucin-domain containing-3

Expression of Tim-3 by HBV specific T-cells results in decreased production of both IFN-ɣ and TNF-α (76). In chronic HBV, Tim-3 expression occurs more frequently on HBV specific CD8 T-cells compared with other CD8 T-cells within the same individual (77).

As the ability to clear HBV has been associated with a strong virus specific T-cell response, blockade of the co-inhibitory pathways described above may restore HBV-specific T-cell function and enable virus elimination.

1.3.3 Hepatitis B genotypes

The lack of a proof-reading function by HBV reverse transcriptase leads to high rates of viral variation. These viral variants are categorised into different genotypes. Historically there were eight well known genotypes A-H with specific geographic distributions and a further two genotypes, I&J have subsequently been identified (78). Of the frequently encountered genotypes, A is predominantly identified in sub-Saharan Africa, Northern Europe and West Africa, B and C in south Asia and genotype D in Africa, Europe, Mediterranean countries and India (78).

Studies conducted to evaluate the clinical significance of HBV genotypes have predominantly concentrated on individuals of Asian origin with genotypes B and C infection. These studies identified that the prevalence of HBeAg positive chronic HBV was higher in individuals with genotype C disease, with spontaneous seroconversion to anti-HBe occurring more frequently in individuals with genotype B infection (79–81). The authors of these studies concluded that individuals infected with genotype C disease remained in the HBeAg positive phase of disease for longer, associated with high levels of HBV replication and active liver disease, subsequently resulting in higher rates of cirrhosis (79–81).

Studies investigating the relationship between HBV genotype and development of HCC in cohorts of individuals of Asian origin produced slightly more conflicting results. Observational studies including a meta-analysis conducted in Japan, China and Hong Kong concluded that infection with genotype C disease was associated with an increased risk of HCC, with development of HCC occurring at an earlier age (82–84). These findings were supported by an American study conducted in patients awaiting liver transplant (OLTx) (85). However, in studies conducted by Kao and Chen et al in Taiwan, although a higher incidence of HCC was observed in individuals infected with genotype C disease, genotype B was associated with HCC at a younger age with the lesions often occurring in the absence of cirrhosis (86,87). It

has been suggested that the discrepancy in the results of these studies may be due to sub-types of the genotype B virus (88), or, given the multifactorial nature of HCC development, a result of exposure to hepatoxins and/or a family history of hepatoma.

There is a paucity of longitudinal data focussing on disease progression and clinical outcomes in individuals infected with HBV genotypes A and D. Results from studies that have been conducted have produced contradictory results. In two studies conducted in sub-Saharan Africa and India, genotype A disease was associated with a greater risk of developing HCC, compared with non-A genotypes (89,90). Due to the geographical variation in these studies, the findings supported the carcinogenic potential of genotype A virus infection irrespective of host ethnicity. In a retrospective study conducted in Indian subjects infected with HBV by Kumar et al, genotype A was associated with progression to more significant liver disease (91) but this was contradicted in studies by Thakur and Toan where genotype D was associated with more severe liver disease and the development of HCC (92,93).

The quality and quantity of data available for interpretation may account for the differences that have been reported in the consequences of long-term infection with these two genotypes. Pre-existing evidence of reported outcomes for long-term infection with genotypes A and D consist of a limited number of small studies with a retrospective trial design. In these trials, individuals were often recruited after presenting to secondary care for assessment for antiviral therapy; therefore the studies have potentially included biased sample populations.

The larger longitudinal observational studies performed in Asian cohorts with genotypes B and C HBV have provided strong evidence relating to the clinical impact of different genotypes in HBV. Performing studies with similar designs in genotype A and D cohorts would help to determine whether the same differences exist with regards to disease progression and clinical outcomes.

The HepFree trial will provide the opportunity to conduct a longitudinal observational study on an unbiased sample of individuals diagnosed with chronic HBV through targeted testing in a pre-defined 'at-risk' population. Individuals of different genders, ages, countries of origin, ethnic backgrounds and HBV genotypes diagnosed through HepFree will be included and

studied to establish disease stage at the time of screening, disease progression, response to antiviral therapy if treatment is recommended, and long-term clinical outcomes.

1.3.4 Treatment options for hepatitis B

The treatment of acute and chronic HBV varies significantly. Treatment options for acute HBV are predominantly supportive, treating symptoms that arise as a result of infection. The use of antiviral agents in acute infection is reserved for individuals who clinically progress to fulminant hepatitis.

In chronic HBV, the aims of treatment are to prevent progression of the disease and the development of HCC, thereby improving the quality of life of the infected individual. The optimum end point of HBV therapy is serological response, classified either as HBeAg seroconversion or HBsAg conversion, the latter of which signifies virus eradication. HBsAg clearance does not occur frequently, therefore HBeAg clearance to anti-HBe with subsequent HBV DNA suppression and resultant improvement in biochemical and histological parameters are more realistic and achievable end points of therapy.

Parameters taken into account when considering HBV therapy initiation include VL, ALT level and histological fibrosis stage. Expert opinion regarding the degree of ALT elevation that should prompt consideration of treatment varies. Table 1 summarises treatment recommendations published by three expert groups. Currently the two main treatment options available for individuals with chronic HBV are forty-eight weeks of response guided therapy with pegylated interferon or long-term therapy with a nucleoside anologue (NA).

Table 1: International guidelines for treatment of HBV

A summary table containing recommendations for treatment in chronic HBV from EASL, AASLD and APASL.

International guideline	HBeAg positive HBV	Anti-HBe positive HBV	HBV associated cirrhosis
EASL (32)	HBV DNA >2.0 x10^3IU/mL and/or ALT >ULN with histological evidence of moderate to severe disease on liver biopsy	HBV DNA>2.0 x10^3IU/mL and/or ALT>ULN with histological evidence of moderate to severe disease on liver biopsy	Compensated Any detectable level of HBV DNA. Decompensated Any detectable level of HBV DNA.
AASLD (94)	HBV DNA>2.0 x 10^4U/mL and ALT > 2 x ULN. *Consider liver biopsy in cases of:* *HBV DNA >2.0 x 10^4U/mL with ALT < 2 x ULN in patients aged > 40 or individuals with a family history of HCC and commence treatment in cases of histological evidence of significant disease*	HBV DNA >2.0 x10^3IU/mL and ALT >2 x ULN. *Consider liver biopsy in cases of:* *HBV DNA >2.0 x10^3IU/mL and ALT > ULN and commence treatment in cases of histological evidence of significant disease*	Compensated HBV DNA>2.0 x10^3IU/mL *Consider treatment in cases of:* *ALT > ULN and HBV DNA <2.0 x10^3IU/mL* Decompensated Any detectable level of HBV DNA.
APASL (95)	HBV VL >2.0 x 10^4U/mL and ALT > 5 x ULN or HBV DNA > 2.0 x 10^4U/mL and ALT 2-5 x ULN or HBV DNA >2.0 x 10^4U/mL and ALT < 2 x ULN but with evidence of moderate to severe inflammation or fibrosis on liver biopsy in individuals aged > 40.	HBV VL > 2.0 x 10^3IU/mL and ALT > 2 x ULN for 3-6 months or with concerns about hepatic decompensation or HBV >2.0 x 10^3IU/mL and ALT < 2 x ULN with evidence of moderate to severe inflammation or fibrosis on liver biopsy.	Compensated HBV DNA > 2000IU/mL Decompensated Any detectable level of HBV DNA.
EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; APASL: The Asian Pacific Association for the Study of the Liver; >: more than; <: less than.			

1.3.4.1 Pegylated interferon

Interferons, because of their potent antiviral, antiproliferative and immunomodulatory effects are a viable therapeutic option in the treatment of both HBeAg positive and anti-HBe chronic HBV. The two major advantages of treatment with interferon therapy are that it is associated with a greater chance of HBsAg clearance when compared to treatment with a NA, and secondly that therapy is for a finite amount of time. Interferon is administered in accordance with strict protocols that advise the monitoring of on-treatment surface antigen levels and include stopping-rules in cases of non-response.

Pegylated interferon (peg-IFN) is considered for use in individuals with evidence of active viral replication in combination with an elevated ALT level and histological evidence of active disease on liver biopsy. Active viral replication is defined as a HBV DNA level of greater than 20,000 IU/mL in cases of HBeAg positive disease and a VL of greater than 2,000IU/mL in individuals with anti-HBe disease (32).

Treatment response to peg-IFN is defined by either seroconversion to anti-HBe, a reduction in quantitative HBV DNA level or HBsAg seroconversion. Treatment outcomes can be observed either at completion of forty-eight weeks of therapy or within twenty-four weeks of treatment cessation. The efficacy of peg-IFN, used as both a single agent and in combination with lamuvidine has been compared in several large multicentre studies (96,97). In the study by Janssen et al, HBeAg positive participants were assigned to treatment either with peg-IFN monotherapy or interferon in combination with lamuvidine (96). HBeAg loss occurred in approximately one third of patients treated, with no significant difference in the rates of clearance observed between the monotherapy and combination therapy cohorts (96). Here, HBsAg loss occurred in seven percent of participants, again no superior outcome was observed in the combination therapy cohort (96).

In a further study of 814 patients with HBeAg positive disease conducted by Lau et al, participants were randomised to three treatment arms and observed for outcomes. The treatment arms were peg-IFN monotherapy, interferon with lamuvidine and lamuvidine monotherapy (97). Suppression of viral load occurred more frequently in individuals that received combination therapy, however HBeAg seroconversion twenty-four weeks after treatment cessation was observed most frequently in the cohort of participants receiving Peg-IFN monotherapy, occurring in thirty-two percent of cases (97). In this trial, surface antigen

clearance was observed in three percent of all participants receiving peg-IFN either as monotherapy or in combination with lamuvidine (97).

In a clinical trial, designed to assess response to peg-IFN therapy in individuals with anti-HBe disease (98), peg-IFN was compared to lamuvidine. Outcomes measured included normalisation of ALT level and reduction in VL to less than 20,000 IU/mL. Superior outcomes were observed in the peg-IFN monotherapy cohort with ALT normalisation and HBV VL reduction observed in fifty-nine and forty-three percent of cases respectively, compared to forty-four and twenty-nine percent in the lamuvidine monotherapy cohort (98). Loss of HBsAg occurred in three percent of participants that received peg-IFN therapy, with no cases of viral clearance observed in the lamuvidine monotherapy cohort (98).

Factors associated with virological and biochemical response to interferon include female gender, young age, high pre-treatment ALT in combination with low pre-treatment HBV VL and genotype A, B and C disease (99,100). Individuals infected with genotype D have a less favourable response to peg-IFN therapy (101).

1.3.4.2 Nucleos(t)ide analogues

Nucleos(t)ide analogues (NAs) are the other main class of agents used in the treatment of chronic HBV. Their mode of action is inhibition of HBV DNA polymerase activity, thereby suppressing viral replication. NAs have no impact on existing cccDNA reservoirs within infected hepatocytes. Five NAs have been approved for the treatment of chronic HBV and due to their optimum resistance profiles, the two main agents used in the UK are tenofovir and entecavir. Treatment response to NAs is defined as an undetectable HBV DNA level by polymerase chain reaction (PCR) assay (32).

NAs are favourable compared to peg-IFN in terms of dosing regimen, side effect profile and patient tolerance. However, treatment, once initiated is often long-term and there is potential for the emergence of drug resistance mutations due to the rapid replication rate of the virus coupled with the lack of an effective proofreading mechanism as discussed previously. A finite treatment regimen with NAs may be considered for individuals with HBeAg positive disease as the indication for treatment, in cases of seroconversion with

subsequent normalisation of serum ALT and reduction in VL to less than 2,000IU/mL (32). Sustained off-treatment response rates following HBeAg seroconversion with NAs vary considerably though depending on the trial reviewed. High durability of seroconversion has been reported in follow-up studies conducted by Dienstag and Poynard et al (102,103). One of these studies however is only available for review in abstract format. Conversley, high relapse rates have been reported in cases of NA treatment withdrawal in studies by Song and Reijinders et al. The authors of these studies concluded that seroconversion as a result of NA therapy is a transient rather than permanent event (104,105). Higher off-treatment success rates were observed in studies performed in Western countries with relapses observed more frequently in Asian populations suggesting that HBV genotype may impact on long-term outcomes observed in the setting of NA therapy. In addition to this, the length of consolidation therapy with NAs varied between the studies and this may have contributed to the differences observed. Finally, the definition of relapse varied between studies, with some only classifying relapse as recurrence of HBeAg positive disease, not taking into account the presence of a detectable HBV VL after withdrawal of therapy.

HBsAg clearance has been documented in individuals receiving long-term NA therapy, although this outcome does not occur as frequently as in cases treated with peg-IFN. A retrospective study of long-term clinical outcomes in individuals receiving NA therapy observed an annual seroclearance rate of 0.33% (106). It is debatable whether HBsAg loss experienced with NA therapy truly represents viral clearance. In this study, nearly one quarter of patients with negative HBsAg status had on-going low level detectable HBV (106). This finding however is not solely observed in cases treated with NA, with comparable findings observed in cases of spontaneous HBsAg clearance (107,108). This finding suggests that HBsAg loss observed in the setting of NA therapy actually reflects a decrease in surface antigen production as a result of suppression of viral replication. Independent of surface antigen status, long-term treatment with NA has been associated with an improvement in histological fibrosis score and reversal of cirrhosis has been observed (109–111).

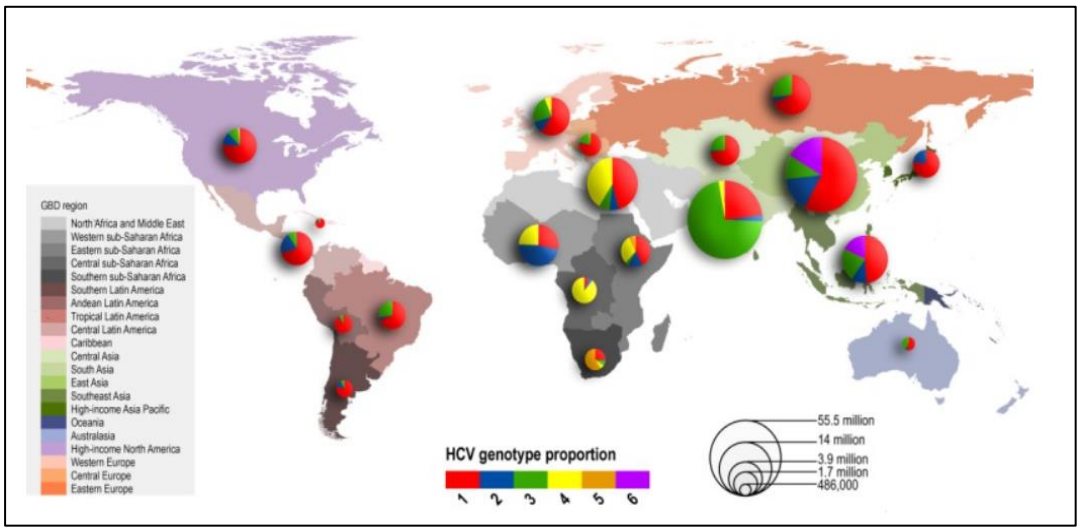
1.4 Hepatitis C

With an estimated 130-170 million cases of infection worldwide, chronic HCV is a significant global health problem (2). HCV has a high predilection for establishing long-term infection, resulting in persistent hepatic inflammation that culminates in liver cirrhosis with or without development of HCC. In developed countries, HCV related disease is now the most common indication for OLTx (112). Development of highly effective antiviral therapies have revolutionised the treatment of a disease that for more than two decades, with the exception of interferon, had very few therapeutic options. Unlike HBV, a vaccine to reduce the spread of disease is yet to be developed.

1.4.1 Discovery of the virus

Hepatitis C, initially referred to as Non-A Non-B hepatitis, was discovered in 1989 following the emergence of a high number of sero-negative cases of hepatitis, observed predominantly in blood transfusion recipients and people who injected drugs (PWID)(113). The complete genome was coded in 1991 and six phenotypically distinct virus genotypes were identified. Multiple quasispecies of the HCV virus exist however, due to errors made by the viral-RNA dependent RNA polymerase during replication (114). Worldwide, genotype 1 is the most prevalent strain of virus, accounting for up to forty-six percent of all HCV infections (115). Genotypes 1, 2 and 3 are predominantly responsible for cases of HCV infection in the United States of America, Australasia and Europe (115). Genotype 4 is prevalent in North Africa and the Middle East, genotype 5 in South Africa and genotype 6 in individuals residing in South East Asia (115).

Figure 2: The global distribution of HCV genotypes



A map depicting the relative prevalence of each HCV genotype by global burden of disease (GBD) region. The size of the pie charts is proportional to the number of seroprevalent cases as estimated by Hanafiah et al (116). Image reproduced from and credited to Messina et al (117).

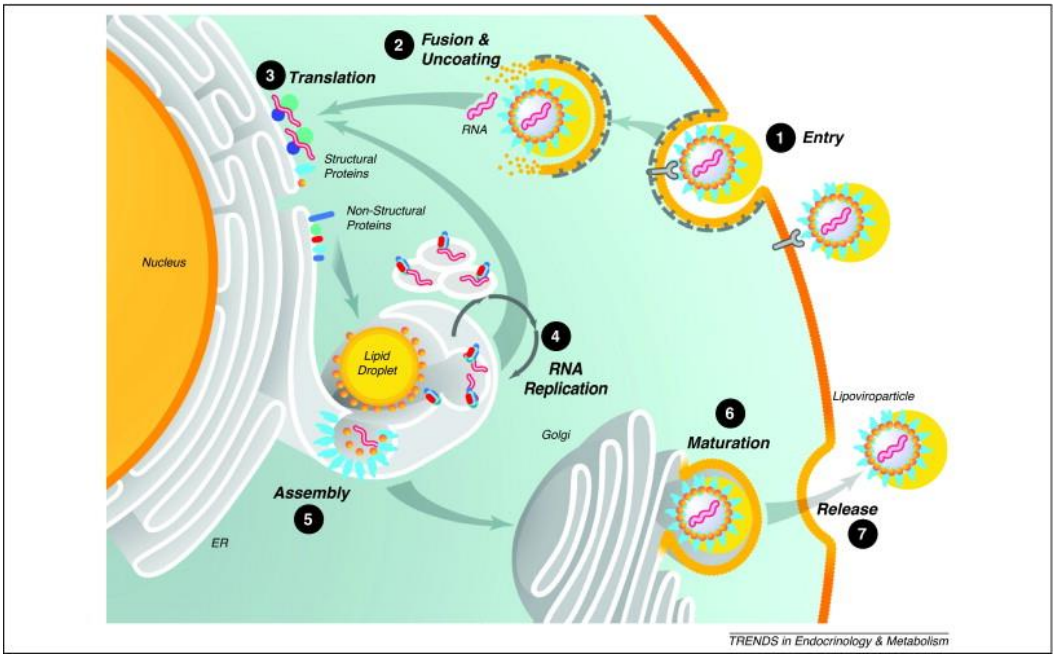
1.4.2 Hepatitis C virus lifecycle

Hepatocytes are the host cells predominantly used by HCV for replication, however replication may also occur in peripheral blood mononuclear cells (118). HCV is comprised of a nucleocapsid core surrounded by a host derived membrane containing the envelope 1 (E1) and envelope 2 (E2) glycoproteins that mediate cell entry (119). Host cell entry is through a complex interaction involving glycosaminoglycans, the low density lipoprotein receptor, the high density lipoprotein receptor scavenger receptor class B type 1, tetraspanin CD81 and tight junction proteins claudin-1 and occludin (120).

Once inside the cell, HCV dissolves its outer coating, releasing a single positive strand of RNA into the cell cytoplasm, this travels to the rough endoplasmic reticulum (RER). Ribosomal subunits associated with the RER serve as translation units, converting the positive strand viral RNA genome into a single large polyprotein of approximately 3011 amino acids. The polyprotein is cleaved by host and viral proteases to produce three structural and seven non-structural (NS) proteins (121). The primary function of the NS proteins is to support viral replication. Non-structural 4B protein (NS4B) with non-structural 5A protein (NS5A) are primarily responsible for formation of the site of HCV viral replication by assembling the membrane associated replication complex responsible for synthesising RNA and then by recruiting the genomic RNA into the complex. Although all NS proteins are essential for HCV replication, NS5B encodes the RNA-dependent RNA polymerase. During viral replication, a negative strand HCV RNA is produced from the positive strand RNA. These combine to form a double stranded intermediate that serves as a template for the production of further copies of the viral genome. The new positive strand RNA is then packaged to form new HCV virions that mature in the host cell golgi apparatus prior to release from the hepatocyte by exocytosis.

Rapid viral replication in addition to a high error rate in the NS5B coded RNA-dependent RNA polymerase results in mutations and a heterogeneous collection of virus quasispecies within each viral genotype (122). Mutations occurring in the hypervariable region of the genome that code for the HCV envelope proteins result in failure of the host T-cells to respond to new virus epitopes which in turn results in high rates of chronic infection through a phenomenon known as original antigenic sin (123).

Figure 3: Hepatitis C virus replication



A diagram demonstrating a replication cycle of HCV as described in the text above. Image taken from 'Unique ties between hepatitis C replication and intracellular lipids' with full credit to Herker & Ott (124).

1.4.3 The epidemiology of hepatitis C

1.4.3.1 Worldwide prevalence

For a multitude of reasons, the global prevalence and true extent of the associated burden of disease related to HCV will probably never be established. The documented global prevalence of HCV derived from reviews of published data is two to three percent (115). Several factors influence the validity of results derived from HCV prevalence studies, and these are discussed below. Firstly, in prevalence studies, screening assays for antibodies to hepatitis C (anti-HCV) form the basis of testing. The presence of anti-HCV is not diagnostic for chronic HCV, it remains positive in the setting of both spontaneous viral clearance and eradication following administration of antiviral agents (125). The use of this test is therefore likely to overestimate the prevalence of disease in the populations approached for testing (126). Prevalence studies that perform PCR testing to confirm chronic infection in individuals with a positive anti-HCV test therefore more accurately reflect the true magnitude of the HCV pandemic. The second factor influencing results relates to the type of immunoassay used by prevalence studies. Advances in medicine have resulted in improved sensitivity of immunoassays used to screen for HCV. Anti-HCV prevalence therefore may have been overestimated with the use of first generation immunoassays (127). In addition to this, any prevalence estimates derived from retrospective studies performed on stored sera need to be interpreted with caution due to the increased reporting of weakly positive antibody tests in 'aged' blood samples (128). Currently prevalence studies use third generation immunoassays to screen for anti-HCV and these demonstrate both a high sensitivity and specificity (129–131).

Conversely, as opposed to over-estimating prevalence, historically, prevalence studies may have underestimated the true burden of disease predominantly because of the cohorts of individuals selected to participate in testing. There are a paucity of published studies focusing on HCV prevalence in high-risk populations, namely in PWID and incarcerated individuals (132). One key example of this is prevalence estimates of chronic HCV infection in the USA in a landmark paper from the NHANES III study by Alter et al. The sample population failed to include either homeless or incarcerated individuals and therefore investigators are likely to have underestimated the true prevalence of disease in the American population (133). Another factor impacting on accurate prevalence reporting relates to the insidious onset and often asymptomatic nature of infection with HCV that prevents prevalence studies for chronic disease being conducted prospectively using individuals presenting with acute infection (134).

Variations in both geographical and temporal trends of chronic HCV infection have been identified by studying infected populations originating from different areas of the world (135). In America, NHANES III, a large population based study conducted between 1988-1994, identified that over half of all chronic HCV infections affected individuals aged between thirty and forty-nine who were therefore born between 1945-1965 (133). The high prevalence of disease observed in this age group indicated that the risk of HCV infection was greatest in the relatively recent past with transmission occurring in young adults either through IVDU or high risk sexual intercourse.

The second pattern of infection, observed in China, Italy, Japan, Spain and Turkey identified cases of infection predominantly in individuals of advancing age with low prevalence rates observed in children and young adults. When investigated in Japan, the seroprevalence in individuals aged less than twenty was very low, less than one percent compared to more than two percent in subjects aged over fifty-five (136). This finding suggested that transmission of HCV started in the 1930s, with infection transmitted through IVDU, unsafe medical procedures and blood transfusions (136).

The third pattern observed was high rates of infection across all age groups. One key example of this was in Egypt. The homogeneity of HCV subtypes in Egypt reflected rapid spread of the virus over a very short period of time, likely related to public health initiatives introduced to control the spread of schistosomiasis. This mass immunisation campaign has subsequently been described as the world's largest example of iatrogenic transmission of a blood-borne pathogen (137–139).

1.4.4 Routes of infection

The routes of transmission of HCV vary depending on the population studied. In developed countries, transmission of the virus is predominantly through injecting drug use. In developing countries however, unsafe medical practices including the use of contaminated healthcare equipment and the transfusion of unscreened blood products are implicated in the spread of HCV.

1.4.4.1 Hepatitis C in people who inject drugs

Globally, ninety percent of new HCV infections are attributed to IVDU (140). International estimates of the incidence of HCV infections in PWID range from eleven to forty-two per one hundred person years, highlighting this as an important risk factor for HCV acquisition (141–143). Independent predictors of HCV infection in PWID include new injectors, in particular individuals with an injecting history of less than twelve months, female gender, a partner who also injects drugs, use of shared needles, assistance required to inject, commercial sex work, incarceration, and concurrent use of intravenous cocaine (141-143). The geographic location of each study, the age of individuals recruited, the duration of each person's injecting history and changing patterns in injecting behaviours are likely to be responsible for variations in the incidence of HCV infections observed in these studies. A systematic review and meta-regression of published literature pertaining to HCV infection in PWID residing in developed countries estimated a prevalence of infection (anti-HCV positive) of 32.02% [95% CI: 25.31%, 39.58%] after twelve months of injecting and 53.01% [95% CI: 40.69-65.09%] after five years of injecting drug use (144).

1.4.4.2 The transfusion of unscreened blood products

Recommendations from The World Health Organisation (WHO) are that globally, blood transfusion related activities including collection, testing, processing, storage and distribution should be coordinated at a national level through integrated blood supply networks. These networks, governed by national blood policies and legislative framework would ensure consistency in the quality and safety of blood and blood products. The WHO Global Database on Blood Safety (GDBS) was established to address concerns about the availability, safety and accessibility of blood transfusions. The GDBS collects and analyses data on blood safety with the objective of improving blood transfusion services globally. In 2013, seventy-three percent of countries submitting data for analysis had a national blood policy, and sixty-five percent had specific legislation for the safety and quality of blood transfusions. Of the one hundred and eight countries with specific legislation in place, seventy-nine percent were classified as high-income, sixty-four percent middle-income and forty-one percent low-income.

As part of its policies on blood safety, the WHO recommended that mandatory testing for human immunodeficiency virus (HIV), HBV, HCV and syphilis be performed on all blood donations prior to use. Data obtained from one hundred and fifty-six countries through the GDBS identified that sixteen countries were still not able to screen all donated blood for one or more of the above infections (145). The most commonly reported barrier to screening for

infections was the irregular supply of kits to perform testing (145). In high-income countries, eighty-one percent of blood screening laboratories were monitored through external quality assessment schemes, compared to fifty-five percent in middle-income countries and as few as thirty-four percent in low-income countries (145). These data support the transfusion of unscreened blood products as one of the major causes of HCV infection in low-income or developing countries

Table 2: Prevalence of transfusion-transmissible infections in blood donations

The prevalence of transfusion-transmissible infections in blood donations in high, middle, and low income countries, reproduced from WHO fact sheet: Blood safety and availability (145).

	HIV Median, range	HBV Median, range	HCV Median, range
High-income countries	0.003% (0.001%-0.040%)	0.030% (0.008% – 0.180%)	0.020% (0.003% – 0.160%)
Middle-income countries	0.120% (0.020% – 0.340%)	0.910% (0.280% – 2.460%)	0.320% (0.090% – 0.690%)
Low-income countries	1.080% (0.560% – 2.690%)	3.700% (3.340% – 8.470%)	1.030% (0.670% – 1.800%)

1.4.4.3 Unsafe medical practices

Historically, in developing countries, medical therapies were commonly administered using injections, with data suggesting that the number of injections administered per person per year ranged between 1.2-8.5, with a mean of 1.5 per annum (146). In this study, in the majority of cases, the indication for injection therapy was often unjustified (146). Despite increasing knowledge about HCV, misconceptions regarding injection safety, repeated use of medical equipment without sufficient sterilisation and poor sharps waste management still exist in low-income countries (147).

Injection therapy was considered to be 'the gold standard' for medicine administration in low-income countries. The reasons for this were public perception regarding the efficacy of injection therapy, increased income attached to injection therapy and the use of injections by

traditional and untrained healthcare workers (146,148). The most powerful example of the relationship between unsafe injections and transmission of HCV was observed in Egypt following parenteral anti-schistosomiasis therapy (138). The findings of this study were supported by a case-control study performed in Pakistan. Here, a significant association was identified between injection use and positive anti-HCV status. One limitation of the study was the authors collected information on exposure to HCV after participants had been informed of their anti-HCV result and this may have resulted in re-call bias (149).

1.4.4.4 Sexual and vertical transmission

Large prospective studies that have been performed in heterosexual couples in monogamous relationships confer that risk of sexual transmission of HCV is low (150, 151) In the HCV partners study, new cases of anti-HCV were discovered in less than five percent of partners included (148). In forty percent of individuals included in the study that had developed antibodies to HCV, the genotype or subtype isolated differed from that of their partner indicating that the infection must have been acquired via an alternative route (151). Another prospective study that recruited more than eight hundred monogamous heterosexual couples identified only three new cases of anti-HCV. In all cases, the viral isolate was not consistent with sexual intercourse as the mode of transmission (150). Factors increasing the risk of transmission of HCV include promiscuity, a history of sexually transmitted infections, intercourse without condoms and co-infection with HIV (152-155).

A systematic review and meta-analysis of twenty studies of pregnant women with chronic HCV infection determined that the risk of vertical transmission of HCV was approximately five percent in children born to HCV positive, HIV negative mothers and ten percent in children born to HIV/HCV co-infected mothers (156).

1.4.5 The natural history of hepatitis C

1.4.5.1 Acute infection

Acute infection with HCV, much like HBV, is either asymptomatic or marked by vague constitutional symptoms including malaise and loss of appetite. Symptomatic acute infection with jaundice occurs in approximately fifteen percent of cases. The silent onset of HCV renders studies relating to the acute phase of infection and rates of persistence extremely challenging, with selection bias likely to occur and impact the results obtained. In the majority of cases, HCV infections are detected during post exposure surveillance (134).

Laboratory diagnosis of HCV is performed using two classes of assays; serologic and molecular. Serologic assays detect anti-HCV with a high degree of sensitivity (129). In acute infection, anti-HCV rises at approximately week eight; therefore this is not the test of choice for diagnosis in the initial weeks following exposure to the virus. However, once detectable anti-HCV remains positive throughout all subsequent stages of infection including cases of chemical eradication or spontaneous clearance (128). During the first two weeks of infection, HCV RNA is present in the blood, rising rapidly up to a level of 10^8IU/mL by week eight (128). Chronic infection is confirmed by detection of HCV RNA in blood six months after the episode of acute infection.

Detection and quantification of HCV RNA is performed with molecular assays. The COBAS-TaqManHCV test version 2.0 (Roche Molecular Systems, Pleasanton, CA) targets the highly conserved 5' non coding region of the HCV genome, generating amplification products detected real-time by a sequence specific TaqMan probe during amplification.

1.4.5.1.1 Factors influencing spontaneous clearance of HCV

As discussed previously, research to establish the rates of spontaneous clearance of HCV in individuals is hampered by the asymptomatic nature of the acute phase of infection. Studies conducted, attempting to establish the rates of spontaneous viral clearance have produced a wide range of results, suggesting that both host and environmental factors including the route of acquisition influence viral clearance. In one study, 173 out of 632 individuals cleared HCV during twelve months of follow-up, with higher rates of clearance observed in female

subjects (157). In a second study following a heterogeneous cohort of sixty-seven individuals with acute infection, a spontaneous clearance rate of eighteen percent was identified. In this study again, spontaneous eradication was seen more frequently in female subjects (158). Studies conducted in homogenous groups of infected individuals - pregnant women receiving contaminated anti-D immune globulin during pregnancy and children with post-transfusion associated hepatitis demonstrated even higher rates of spontaneous viral clearance. In these studies, only fifty-five percent of individuals with anti-HCV had evidence of chronic infection (159, 160). The factors identified that influence spontaneous clearance of HCV are discussed below.

1.4.5.1.2 Age at the time of infection

The impact of age on developing chronic infection has been investigated in several studies. In the NHANES III study, detection of RNA positive HCV in the anti-HCV positive population aged over twenty was 75.6% [95% C.I: 67.3-84.9%] compared with 30.1% in individuals aged less than twenty [95% CI: 9.8-92.8%]. A small sample size is likely to be responsible for the wide confidence interval and raises suspicion about the validity of this finding; the prevalence of chronic infection may not be as high as two and a half times in the older age group (133). The association between age and chronicity of HCV infection was further demonstrated in a larger cohort in the DIONYSOS study. Persistence of HCV infection in subjects aged less than forty-five years of age was fifty-six percent compared to seventy-two percent in those aged over forty-five (161).

1.4.5.1.3 Gender

Conflicting evidence exists regarding the role that gender plays on the rate of persistent infection in individuals with HCV. Two observational studies in females exposed to contaminated anti-D immune globulin during pregnancy identified that only fifty-five percent of subjects with positive anti-HCV had chronic HCV infection (159, 162). Female gender was also associated with spontaneous clearance in studies performed on heterogeneous cohorts (157, 158). Larger population studies however have produced conflicting results. In these follow-up studies, gender was only demonstrated to be significant in non-Hispanic subjects (133). One explanation for the high rate of spontaneous clearance in females in the infected anti-D cohort may be the specific characteristics of the individuals. Oestrogen has been associated with increased rates of viral clearance in the setting of interferon therapy in women aged less than forty years of age (163). In pregnancy, oestrogen is a key hormone responsible for uterine expansion, relaxation of pelvic ligaments and the prevention of

uterine contraction. In addition to this, in both of the anti-D immune globulin follow-up studies there was no male sex cohort for viral clearance comparison.

1.4.5.1.4 Ethnicity

Black ethnicity has been associated with statistically significant lower rates of viral clearance (133). In the NHANES III population study, the prevalence of HCV RNA positivity among anti-HCV positive participants in non-Hispanic blacks was eighty-six percent compared to sixty-seven percent in non-Hispanic whites (p=0.02)(133). In a study of PWID in Baltimore, again higher rates of viral clearance were observed in white ethnic groups, with chronic HCV infection identified in ninety-five percent of African-Americans included (164).

The higher rates of viral persistence in Black and African-American ethnic groups is related to the single nucleotide polymorphism rs12979860 upstream of the IL28B gene (165). Enhanced viral clearance and response to treatment is observed in individuals with the IL28 CC genotype, with individuals being three times more likely to clear HCV compared to the other genotypes CT/TT. The C allele is less frequently observed in individuals of African descent, explaining the higher rates of persistent infection (165).

1.4.5.1.5 Immune status

Co-infection with HIV increases the rate of viral persistence in HCV. In a study of individuals with altered immune status, namely co-infection with HIV paired with low CD4 cell counts of less than 200 x 10^6/L, observed episodes of spontaneous viral clearance of HCV were lower compared to non-infected subjects [odds ratio (OR) 2.19 CI 1.26-3.47] (166).

1.4.5.1.6 Symptomatic acute infection

The final predictor of spontaneous clearance is the presence of jaundice complicating the acute phase of infection (162, 164).

1.4.5.2 Chronic HCV infection

Chronic infection with HCV causes persistent hepatic inflammation resulting in parenchymal liver damage characterised histologically by fibrosis score. The end point of chronic infection with HCV is liver cirrhosis with or without the development of HCC. In the context of cirrhosis secondary to HCV, the annual risk of HCC development is between one and four percent (167, 168).

The natural history of HCV is still largely unknown. The insidious onset and often asymptomatic nature of HCV makes it difficult to perform prospective longitudinal follow-up studies in order to determine fibrosis progression. Results obtained from retrospective studies that have attempted to establish fibrosis progression have produced conflicting results and this may be due, in part to the characteristics of participants recruited. Published data on fibrosis progression to cirrhosis varies significantly from between two to three percent to fifty-one percent after a duration of twenty years of infection (162,169). One possible explanation for the large difference in reported progression rates are the study populations. In the study by Tong et al, individuals infected with HCV from blood transfusions were recruited after presenting for assessment to a tertiary hepatology unit, implying a cohort consisting of more unwell, symptomatic individuals. In this study, the mean age at the time of infection was thirty-five, established by participant recall (169). Wiese et al studied fibrosis progression in a cohort of women with very similar characteristics, exposed to HCV during pregnancy. These individuals were diagnosed with HCV after been recalled for testing due to the potential risk of infection from contaminated blood products, thereby implying a more asymptomatic cohort, unlike in the study by Tong et al (162).

A number of modifiable and non-modifiable risk factors that result in an accelerated progression of fibrosis have been identified and include advancing age at the time of infection, male gender, hepatic steatosis and insulin resistance, co-infection with HBV or HIV, and excess alcohol consumption (170-172). Genotype 3 infection has also been associated with an accelerated course of fibrosis (173).

Data used to estimate fibrosis progression has been obtained from studies that have used either a single or paired liver biopsy design (170,174,175). Retrospective studies using data from single liver biopsies, with the duration of infection established by participant recall have suggested that progression of fibrosis in HCV infection is linear with an increase in fibrosis of between 0.12 and 0.19 units per year (170,174). In these studies, the median duration of time between infection and the onset of cirrhosis was thirty years in the absence risk factors for accelerated progression (170,174). In the single liver biopsy studies from which these conclusions were drawn, an assumption was made that the rate of progression of fibrosis in HCV infection is consistent, however this is not supported in other single and paired liver biopsy studies (176–178). A prospective study that compared data obtained from paired liver biopsy samples taken from a group of individuals not treated for HCV strongly disagreed with the concept that fibrosis progression in HCV is linear and furthermore, that it can be predicted from duration of infection with the use of a single liver biopsy (175). In the study by Ryder et al, the two independent factors that influenced fibrosis progression were the presence of fibrosis on the index biopsy and the age of the individual at the time of infection (175).

In addition to hepatic dysfunction, significant morbidity and mortality has been associated with extra-hepatic manifestations in HCV. A large Australian community-based study conducted retrospectively in individuals with HCV identified an increase in all-cause as well as in liver-related mortality in the cohort infected with HCV compared with the general population of New South Wales (179). In this study, death from liver-related causes was identified more frequently in individuals of advancing age, and this is likely to be related to the duration of infection with HCV. Conversely, in young adults, especially in females infected with HCV, the risk of dying from complications of drug use exceeded liver-related deaths. The findings of this study are consistent with other studies looking at outcomes in HCV infected PWID (180, 181).

The increased number of liver-related deaths in individuals of advancing age identified by Amin et al supports the use of antiviral therapies in these age groups to prevent complications associated with long-term infection (179). There were however limitations associated with the data collected and presented in this study. Firstly, individuals with HCV were only followed by investigators for five years; this period is inadequate in duration to observe all complications associated with HCV. Secondly, the study design was retrospective, therefore all data collected for interpretation was death registry data, increasing the possibility of both incomplete and inaccurate data sets.

Through targeted testing for viral hepatitis in primary care, HepFree will identify a cohort of individuals, infected with HCV that are unaware of their diagnosis, thereby implying an asymptomatic cohort. All individuals enrolled in HepFree found to have chronic HCV infection will undergo fibrosis assessment at the time of diagnosis with subsequent long-term follow-up for clinical outcomes. The data collected from this screening trial will augment the pre-existing evidence base both for fibrosis progression and morbidity and mortality associated with chronic HCV.

1.4.6 Quality of life in hepatitis C infection

Historically, chronic HCV infection was thought to be predominantly asymptomatic, with signs and symptoms arising only in cases of advanced disease complicated by the presence of cirrhosis (182). This differs from other diseases that are characterised by the presence of persistent inflammation. The significance of extra-hepatic manifestations in chronic liver disease of other aetiologies, in particular the impact of fatigue on quality of life in primary biliary cirrhosis (PBC) has been recognised. In PBC, it is widely recognised that symptoms experienced by patients correlate poorly with both biochemical markers of severity and the degree of hepatic fibrosis present (183–185). A plethora of studies exist that have identified symptoms in individuals infected with HCV. These studies, the symptoms reported and the subsequent impact on quality of life are discussed below.

1.4.6.1 Fatigue

Fatigue is the most commonly reported symptom in individuals with chronic HCV (169,186–188). The subjective nature of fatigue, combined with the lack of specific therapies available for treatment makes it arguably one of the more distressing manifestations associated with the disease (189). In observational studies of individuals infected with HCV, high rates of fatigue have been reported; 67% of individuals infected with HCV from contaminated blood and 81% infected from contaminated anti-D immune globulin respectively (159,169). In a study assessing symptoms with the use of questionnaires, performed in a hepatology outpatient department, identified that fatigue in individuals with HCV was more significant compared to liver disease of other aetiologies (186). In a large study by Poynard et al, fatigue was more prevalent in females of advancing age, but there was no correlation identified

between symptom severity and the degree of histological fibrosis observed (187). The major limitation of the studies performed to investigate fatigue in HCV is the absence of a control group for comparison.

1.4.6.2 Cognitive impairment

Hepatic encephalopathy (HE), first described by Sherlock et al, is the neuropsychiatric syndrome most commonly associated with hepatic failure (190,191). Latent sub-clinical minimal hepatic encephalopathy (MHE) is the term used to describe the constellation of symptoms and signs characterised by selective impairments of psychomotor speed, visual perception and attention with persevered verbal ability. MHE can occur in individuals with cirrhosis with no appreciable signs of HE (191,192).

Due to the frequent complaint of 'mental clouding' in the context of chronic HCV infection, studies have attempted to investigate the effects of HCV on cognitive functioning in individuals with both non-cirrhotic and cirrhotic liver disease (193–197). Cordoba et al assessed cognitive functioning by using a series of neurophysiologic tests. In this study, individuals were classified as having either mild disease, compensated or decompensated cirrhosis and the findings obtained in each cohort were compared to healthy controls (196). Exclusion criteria for the study included a history of excess alcohol consumption, psychotropic drug use, illiteracy and marked cognitive impairment. In this study, neurological abnormalities were identified solely in the cohort of individuals with decompensated cirrhosis (196).

The direct effect of HCV on the central nervous system has been investigated in cohorts of individuals that have no evidence of liver cirrhosis. The hypothesis of subclinical cognitive impairment in HCV was studied by performing a series of sensitive electrophysiologic tests of cognitive processing by Kramer et al (195). Findings from this study demonstrated sub-clinical impairment of cognitive brain function in the HCV infected cohort (195). The results obtained occurred independent of the degree of histological or biochemical activity of hepatitis and also independent of the severity of fatigue observed within the same cohort (195). The results of this study were supported by findings from a study by Forton et al, and confirmed that mild cognitive impairment is a feature of chronic HCV infection (193). In these studies, the authors addressed the potential negative effect of a history of substance misuse on

cognitive impairment in addition to the potential negative effects of depression and fatigue; two conditions prevalent in HCV infected populations. Independent of the aforementioned factors, the study detected a decrease in concentration as well as a reduction in working memory speed (193). Within the study design, a sub-group of seventeen individuals with HCV as well as a control group of healthy volunteers underwent further tests with cerebral proton magnetic resonance spectroscopy (MRS). The results of these tests demonstrated significantly elevated choline/creatine ratios in the basal ganglia and white matter of the HCV infected cohort compared to the healthy controls (193). A subsequent imaging study by the same lead author confirmed that chronic HCV results in neurological damage (198) . In this study, MRS was performed on three cohorts of individuals; individuals with chronic HCV with no histological evidence of advanced disease, individuals with evidence of previous exposure to HCV, and a group of healthy controls. Mean myoinositol/creatine levels were higher in HCV positive cohort compared to the healthy control group with a strong association established between elevated levels and prolonged working memory reaction times, p=0.002 (198).

1.4.6.3 Depression

Depression is frequently reported in quality-of-life (QOL) studies performed in individuals with chronic HCV; however there is wide variation in the incidence of symptoms reported depending on the study referred to. In an interview based trial performed in 157 individuals referred to a tertiary Hepatology unit, depression resulting in a reduction in QOL was reported in more than fifty percent of individuals (199). This study population contained a large number of participants with cirrhosis. The authors however stated that no significant difference in depression reporting rates were observed between the cirrhotic and non-cirrhotic subjects interviewed (199). In this study, depression was associated with a reduction in health related quality-of-life (HRQL). A correlation was identified between HRQL scores and both knowledge and understanding of the disease, therefore raising the possibility that depression in HCV arises as a result of fear of the condition and the implications of long-term infection, rather than as a direct effect of the virus itself.

In studies investigating the incidence of depression in HCV by Dwight and Fontana et al, depression was observed in twenty-eight percent and thirty-five percent of individuals respectively. There was a positive correlation observed between the severity of fatigue reported and degree of depression observed (200,201). With the exception of one study,

once again, the lack of a healthy control cohort for comparison was the major limitation of the studies described. The one exception was a large Italian study conducted by Carta et al that demonstrated an increased incidence of depressive disorders in patients with chronic HCV compared to two other cohorts; subjects both chronic HBV and healthy controls (202).

1.4.6.4 Musculoskeletal pain

In a study analysing data collected from 239 questionnaires completed by individuals attending a hepatology outpatient department, the most frequently reported symptom was musculoskeletal pain, in particular backache. Additional symptoms included myalgia, muscle stiffness and neck pain (186). In the HCV cohort interviewed, the incidence of both fatigue and musculoskeletal pain was significantly higher compared to cohorts of individuals with liver disease of other aetiologies (186). In observational longitudinal follow-up studies conducted in individuals infected with HCV during pregnancy in Ireland and Germany, arthralgia and myalgia were also frequently reported (159,162). The results of these studies however do have to be interpreted with caution due to the financial provisions available for individuals with long-term health problems arising as a result of infection with HCV.

1.4.6.5 Health-related-quality-of-life in the setting of chronic HCV

Investigators have used HRQOL questionnaires to explore the impact of chronic HCV on an individual's well-being, including any effects that treatment and subsequent cure might have. Several large studies have identified that irrespective of the severity of liver disease, infection with HCV causes symptoms that result in a reduction in QOL (203,206). Difficulty remains however in determining whether reduction in QOL occurs as a direct consequence of viral infection or whether it is multifaceted, influenced by symptoms, pre-existing knowledge and anxiety surrounding the diagnosis as well as fear about the long-term implications of infection. In a study by Foster et al, the Short Form 36 (SF-36) questionnaire was used to assess the impact of symptoms on QOL in individuals with HCV (207). This study enrolled two cohorts infected with chronic HCV infection, differentiated by the presence or absence of a history of substance misuse. The purpose of this trial design was to address and reduce any potential bias arising from drug-use and any associated behaviours that may have had an adverse effect on QOL, some of which have previously been described(208,209). SF-36 outcomes from participants with HCV were compared to outcomes collected from a cohort of

individuals infected with chronic HBV and a cohort of healthy controls (207). In the two HCV-infected cohorts, scores related to mental and physical health were significantly reduced compared to the non-HCV populations (207). There was only a small difference in QOL observed between the drug-using and non-drug using cohorts (207). The findings of this study, supported by a study conducted by Poynard et al, concluded there was no correlation between QOL reported and the histological degree of inflammation observed in HCV (187). These findings were also supported by studies from Carithers, Davis and Ware et al (203,204,206).

The effects of treatment with peg-IFN and SVR on QOL have been studied (205,210–214). Prior to anti-viral therapy, irrespective of the severity of liver disease, all individuals included in these studies were identified to have a reduction in HRQOL compared to healthy individuals. Marked improvements in both QOL and functioning were observed in individuals that obtained an SVR following treatment. The improvement observed in the SVR cohort was more significant than any changes in QOL noted in the cohorts of individuals that received anti-viral therapy but in whom treatment was unsuccessful (205,210-214).

A study by Rodgers et al however disagrees with the concept that reduction in QOL observed in individuals with HCV arises as a direct consequence of viral infection and therefore improves with eradication of the virus following administration of anti-viral therapy. The Australian study aimed to investigate the impact of pre-existing knowledge of HCV on an individual's perceived QOL and well-being (215). In this study, QOL was assessed in two cohorts of individuals with chronic HCV, one containing individuals aware of their diagnosis and one cohort blinded (215). In the cohort with pre-existing knowledge of their disease status, data obtained from the QOL assessment tools used were comparable to results published by Carithers, Davis, Foster and Ware et al, with a reduction identified in seven out of eight questionnaire domains (203,204,206,207). In contrast to this, in the cohort blinded to their disease status, reduction in QOL was only observed in three domains and importantly, any reduction in emotional or physical health reported by this cohort did not perceive that the reduction impacted on either their overall functioning or on activities of daily living (215).

The reduction in QOL observed in the cohort blinded to their diagnosis, although not as severe, does support the argument that symptoms in HCV do not arise purely in response to psychological distress associated with knowledge of the virus. The study by Rodgers et al did however highlight two major limitations with the other trials reviewed. The first limitation

relates to the sample populations studied. In the trials discussed, all symptom assessment tools and questionnaires were performed in individuals that had been referred to either a secondary or tertiary care centre for assessment. The locations selected for participant recruitment could infer a more 'unwell' population and the prevalence of symptoms in individuals seeking medical care are more likely to be greater than in individuals who have either not yet been referred for specialist input, or in individuals in whom the disease was detected through routine screening based solely on 'risk' of infection. The second limitation was that all questionnaires were performed in cohorts of individuals aware of their diagnosis. The authors have therefore failed to consider the potential psychological impact of a diagnosis of HCV on both symptom and QOL reporting (216).

Although many studies have examined the impact of chronic HCV on individuals diagnosed with HCV no study has, to-date, examined the impact of undiagnosed HCV infection on healthcare utilisation. We hypothesised that if HCV infection per se, rather than knowledge and anxiety regarding the diagnosis, is responsible for the observed changes in QOL then patients with undiagnosed chronic HCV should present to their general practitioners with complaints of fatigue more frequently than uninfected controls. The HepFree study provided a unique opportunity to examine this.

The primary aim of the HepFree sub-study was to explore the impact of undiagnosed HCV on healthcare utilisation in a primary care setting. The sub-study design was a retrospective case-control study. Cases consisted of individuals with a positive test for HCV, identified through targeted testing in high-risk populations in the HepFree trial and controls consisted of individuals that attended for screening and tested negative for both HBV and HCV through HepFree. Controls were matched to cases using the following criteria: age, gender, ethnic origin, country of birth and length of time resident in the UK. This sub-study was unique in its design and aimed to enhance pre-existing knowledge on symptomatology in chronic HCV.

In the sub-study, primary care data including number of GP appointments and presenting clinical complaint were collected for individuals in both cohorts up to the point of enrolment and viral hepatitis testing through HepFree. Similar to the study by Rodgers et al, in the HCV infected cohort, individuals included in the sub-study were blinded to their diagnosis prior to the date that the screening test was performed, giving us the opportunity to explore symptoms that occur in individuals with undiagnosed HCV without having to adjust for either reporter bias, recall bias or having to take into account any potential psychological impact of a

diagnosis of chronic HCV. The HepFree sub-study was also unique in its design because of the location selected for data collection. Previous studies investigating symptoms have been conducted in subjects referred to secondary and tertiary care centres; however individuals included in the HepFree sub-study were identified through 'routine' testing in a presumed healthy population that have risk factors for chronic viral hepatitis.

1.4.7 Treatment of chronic hepatitis C

The goal of treatment in chronic HCV is to reduce both liver related complications including end-stage liver disease and/or HCC in addition to all-cause mortality by achieving a cure, otherwise known as SVR. The definition of SVR is aviraemia twenty-four weeks following completion of antiviral therapy and is considered a cure in more than ninety-nine percent of cases (217). Multiple benefits associated with SVR include a decrease in liver inflammation as reflected by a decrease on serum aminotransferase levels as well as a reduction in the rate of progression of liver fibrosis (218). Treatment and cure has also been associated with a more than seventy percent reduction in the risk of HCC and a ninety percent reduction in the risk of liver- related mortality and transplantation (219,220).

Treatment for HCV consists largely of antiviral agents, with liver transplantation reserved for individuals with end-stage liver disease that either cannot tolerate medical therapy, or those with HCV related complications namely HCC. As discussed, the development of DAAs has revolutionised HCV treatment. In this thesis, treatment options and outcomes pre and post the introduction of DAAs will be discussed.

Prior to 2011, there were limited therapeutic options available for HCV and treatment consisted of peg-IFN and ribavirin. Peg-IFN was used because of its potent antiviral and immunomodulatory properties, however its exact mode of action in treating HCV remains unknown (221). Duration of treatment with these agents varied, depending on genotype and VL in addition to host characteristics including age, race, body mass index (BMI), stage of hepatic fibrosis and presence of co-infection with HIV(221). In the largest paired liver biopsy study of HCV/HIV co-infected individuals, one third of individuals had evidence of fibrosis progression of at least one METAVIR stage at a median interval of two and a half years, and nearly one half of individuals that had no fibrosis on their index biopsy had evidence of histological progression (222).

In 2011, the first generation direct-acting antiviral therapies with NS3 protease inhibitors (PIs) boceprevir and telaprevir were licensed for use in genotype 1 infection. Prior to the era of PIs, genotype 1 was considered the most resistant to medical therapy. Phase III trials conducted using these agents in combination with peg-IFN and ribavirin demonstrated an increase in SVR rates from between forty to fifty percent to between sixty-five and seventy percent making clinicians optimistic about the future treatment of their genotype 1 infected populations (223,224).

1.4.7.1 Hepatitis C treatment: The past

Early treatment with interferon monotherapy provided somewhat disappointing response rates. Twenty-four week SVR rates varied between six to twelve percent in subjects that received six months of therapy and between sixteen to twenty percent in individuals treated for twelve months (225). Combination therapy consisting of the guanosine anologue ribavirin and peg-IFN was the next approved treatment for chronic HCV (226).

Combination therapy was associated with higher SVR rates, ranging between forty-two and forty-six percent in genotype 1 infection and between seventy-six to eighty percent in genotypes 2 and 3 infection (227,228). Duration of treatment with combination therapy was response guided according to VL, with treatment terminated prematurely in the event of either no response in VL, termed null response or an initial response followed by a relapse and subsequent increase in VL(221).The terms that were used in combination therapy treatment are detailed in Table 3. Approximately one-third of individuals who received combination therapy were classified as null responders (221). Poor predictors of response to antiviral therapy included infection with genotype 1 virus, male gender, African American race, advancing age, advanced hepatic fibrosis, IL28 TT genotype and the presence of insulin resistance (229).

Table 3: Responses to combination therapy in hepatitis C virus infection

Definitions used to describe an individual's response to combination therapy with peg-IFN and ribavirin in HCV infection. Original classification credited to Feld & Hoofnagle.

Term	Definition
Rapid Virologic Response (RVR)	Undetectable HCV RNA at week four of treatment. Obtaining RVR was identified as one of the strongest predictors of successful virus eradication with SVR in all gentoypes (230,231).
Extended Rapid Virologic Response(eRVR)	Undetectable HCV RNA level from week four to week twelve.
Early Virologic Response (EVR)	Undetectable serum HCV RNA at week twelve of therapy. Failure to achieve an EVR was identified as the most accurate negative predictor of SVR in individuals receiving combination therapy (230). Failure to achieve an EVR was an indication to prematurely stop combination therapy in genotype 1 infection.
Null response (NR)	Failure to suppress serum HCV RNA by at least 2 log10 by week twelve of treatment. Treatment was discontinued in this group of individuals as soon as this non-response pattern was recognised (232).
Partial response (PR)	A reduction in HCV RNA by at least 2 log10 at week twelve of treatment but detectable levels of HCV RNA at week twenty-four.
Virologic Breakthrough	Detectable HCV RNA in a patient with previous HCV RNA suppression whilst still receiving combination therapy.
End of Treatment Response (ETR)	Undetectable HCV RNA at the end of combination therapy.
Sustained Virologic Response (SVR)	Undetectable HCV RNA levels twenty-four weeks after treatment discontinuation. A twenty-four week SVR represents HCV eradication in 99-100% of patients (233).
Virologic Relapse	Recurrence of HCV RNA in a patient with an end-of treatment response.

1.4.7.2 Treatment indications and side effects

This section refers specifically to side-effects related to HCV treatment prior to the development of DAAs. In the new, rapidly changing landscape of HCV treatment, it is arguably easier to treat infected populations because courses of therapy are shorter, easier to tolerate, and require less monitoring. These desirable qualities do however come at a greater cost to the NHS.

For combination therapy, EASL produced guidance recommending consideration of treatment in all individuals with compensated cirrhosis and without contraindications to peg-IFN therapy (234). Individuals with histological evidence of advanced fibrosis (METAVIR score F3 or above) or those with clinically significant extra-hepatic manifestations of HCV were given priority. These guidelines did not provide comprehensive instructions relating to the timing of treatment in individuals with HCV infection and evidence of minimal fibrosis on histological assessment and with no identifiable risk factors for rapid disease progression.

Contraindications to peg-IFN therapy include pre-existing evidence of uncontrolled depression, psychosis, epilepsy, autoimmune thyroid disease, retinal disease, decompensated liver disease and pregnancy (234). For individuals termed intolerant to peg-IFN, prior to the development of all oral therapies, treatment options were scarce.

1.4.7.3 Combination therapy side effects

The side-effect profiles of peg-IFN and ribavirin are vast, ranging in severity from influenza-like symptoms, headache, fatigue and fever to anaemia, depression and psychosis (235). It is reasonable to suggest that peg-IFN did, and does continue to act as a relative barrier to effective treatment of HCV either because individuals are reluctant to seek treatment because of the perceived side-effect profile or stop therapy prematurely due to side effects experienced (12).

In a large retrospective study documenting adverse outcomes in individuals receiving peg-IFN therapy, thyroid dysfunction, diabetes and psychiatric presentations were the most common non-hepatic disorders observed (236).

The relationship between peg-IFN therapy and development of psychiatric symptoms is well recognised, occurring either de-novo or in individuals with a documented personal history of mental health disorders. In a cohort of individuals followed for adverse events in the setting of peg-IFN therapy, ten discrete episodes of psychiatric disturbance were observed, and all occurred in individuals without a prior personal history of mental health problems (236). An increased risk of recurrence of depression or psychiatric disturbance during peg-IFN therapy has been documented in several studies (237–239). In addition to this, case reports documenting suicide in individuals receiving peg-IFN therapy have been published (236,240).

Conflicting evidence regarding the risk of recurrence or worsening of symptoms in individuals with psychiatric comorbidities does exist. In a study by Schaefer et al, no increased risk of recurrence or exacerbation of symptoms in individuals with a past history of psychiatric disorders was identified (241). The trial design may however have influenced the findings observed. Participants included in the trial were reviewed by a psychiatrist twice a week for the first eight weeks of peg-IFN therapy and once a month thereafter. Any changes in mood identified in trial participants prompted a comprehensive mood assessment to be performed and either antidepressant therapy commenced or psychiatric medication modified. In the trial, the frequency that depressive episodes occurred was not significantly increased in the cohort of participants with pre-existing mental illness compared to the control group, but the severity of the depressive episodes were more significant. The investigators commented that all suicidal thoughts 'disappeared under psychiatric care'. In this trial, intensive psychiatric input, enabling early recognition of symptoms and use of therapeutic agents is likely to have accounted for the outcomes observed.

The role of peg-IFN in the development of type 2 diabetes mellitus (T2DM) in cohorts of individuals with HCV is a little less clear. Insulin resistance is a well-recognised extra-hepatic manifestation of chronic HCV (242). Studies, including a meta-analysis that have explored the relationship between HCV infection and T2DM have demonstrated an increased prevalence of diabetes in individuals with chronic HCV compared to non-infected subjects (243,244). The development of type 1 diabetes mellitus (T1DM) in the setting of peg-IFN therapy has also been described; firstly by Fabris et al, and later by several other authors (245–248). In Japan, a nationwide cross-sectional study identified a prevalence of T1DM of 0.34% among patients receiving peg-IFN therapy with anti-islet antibodies identified in more than ninety percent of cases (249). In addition to the development of T1DM in individuals receiving peg-IFN, other autoimmune disorders including autoimmune thyroiditis, autoimmune hepatitis, rheumatoid

arthritis, systemic lupus erythematous, autoimmune thrombocytopenic purpura and immune mediated dermatological disorders have also been identified (236,250,251).

Observational studies performed in individuals receiving peg-IFN therapy have identified additional non-immune mediated, non-hepatic disorders including cardiovascular disease, seizures, impotence, peripheral neuropathy and haemolytic anaemia (250). In these studies, disorders resolved spontaneously following withdrawal of the drug, and a relationship between the frequency of side effects and both dose and duration of therapy administered to individuals were established (236,250).

The overall incidence of fatal or life-threatening side effects associated with interferon therapy in the Italian cohort were low with the trial authors concluding that the risk of death from peg-IFN was not increased compared to an individual's risk of death from complications related to chronic viral hepatitis in the presence of poor predictors of survival (236).

As the majority of side-effects related to peg-IFN appeared to be duration dependent, the development of newer treatments that resulted in a reduction in the duration of therapy with peg-IFN inevitably resulted in an improvement in the safety profile of the drug.

1.4.7.4 Advances in medical therapy

In 2011, the introduction of first generation NS3 PIs improved SVR rates in adults with genotype 1 infection. The new agents at that time, boceprevir and telaprevir worked by directly inhibiting HCV proteins required for intracellular replication. In both treatment naïve (TN) and treatment experienced (TE) patients, SVR rates with triple therapy were superior to peg-IFN and ribavirin combination therapy, 63-66% and 58.6-66.5% respectively (224,252).

Despite the introduction of triple therapy leading to overall improvements in SVR rates, the side-effect profile as well as the risk of drug-drug interactions and potential for adverse outcomes associated with PI therapy made the management of individuals on anti-viral therapy much more complex (253,254). The introduction of first generation PIs did not herald the start of an era of well-tolerated anti-viral therapy.

First generation PIs inhibit cytochrome P450 3A (CYP3A). When used in conjunction with drugs highly dependent on CYP3A for clearance can result in serious or life-threatening interactions. Because of the significant risk of drug-drug interactions, extra care was required during the assessment period of genotype 1 patients prior to treatment.

Well documented side-effects with PIs included a rash associated with telaprevir therapy and dysgeusia associated with boceprevir (253). In addition to these, anaemia, often multifactorial in origin was commonly observed in individuals receiving treatment.

Further advances in the understanding of the HCV genome resulted in the development of new DAA therapies. These agents target HCV encoded proteins that are vital for virus replication. These agents as well as being better tolerated had superior efficacy against HCV. Due to the rapidly changing recommendations for HCV treatment that are occurring in response to new DAAs, in this section I will discuss the agents that were available for use to treat chronic HCV during the time period that the HepFree trial was active. The four classes of DAAs used were available in both interferon-containing and interferon-free 'all-oral' regimens.

1.4.7.5 Non-structural protein 3 (NS3)/Nonstructural protein 4A (NS4A) protease inhibitors (PIs)

The mode of action of these molecules is inhibition of the NS3/NS4A serine protease enzyme that is involved in the post translational processing and replication of HCV. During HepFree, the agent available for use as part of a combination regimen was simeprevir. Therapy with simeprevir was generally well tolerated, with very few individuals needing to discontinue therapy due to side effects. The two side effects related to the drug include photosensitivity and rash, in addition to mild elevations in serum bilirubin, occurring in response to inhibition of the hepatic transporters OATP1B1 and MRP2 (255).

1.4.7.6 Non-structural protein 5A (NS5A) inhibitors

During HCV replication, NS5A is involved in both viral replication and modulation of the physiology of the host cell (256). Inhibition of NS5A interrupts viral replication, assembly and virus secretion (257). NS5A inhibitors are very well tolerated. In clinical trials using daclatasvir as part of a combination regimen, the most commonly reported side effects were headache, fatigue and nausea ranked mild to moderate in severity (258). The agents that were available for use in combination therapy included ledipasvir and daclatasvir.

1.4.7.7 Non-structural protein 5B (NS5B) inhibitors

NS5B is an RNA-dependent RNA polymerase that initiates complementary negative-strand RNA synthesis. The negative-strand RNA then acts as a template enabling this protein to synthesise positive-strand RNA(259). The molecules developed that inhibit NS5B are classified as either nucleotide polymerase inhibitors (NPIs) or non-nucleotide polymerase inhibitors (NNPIs).

NPIs target the catalytic site of NS5B resulting in chain termination. Once inside the hepatocyte, NPIs are activated through phosphorylation to nucleoside triphosphate. This competes with nucleotides and results in chain termination during RNA replication of the genome. NNPIs induce conformational changes in the NS5B polymerase enzyme by binding to its various allosteric sites. They have a low barrier of resistance and are genotype specific. The NS5B inhibitor available for use was the sofosbuvir. Side effects experienced by individuals using sofosbuvir occurred as a result of concurrent treatment with interferon and ribavirin.

1.4.7.8 Direct acting antiviral treatment regimens

In this section I will review clinical trials that have been conducted in TN and TE individuals using the drugs described above.

1.4.7.8.1 Genotypes 1 and 4

In phase III trials conducted in TN individuals with genotype 1 infection, simeprevir was used in combination with peg-IFN and ribavirin for twelve weeks, followed by either twelve or thirty-six weeks of consolidation therapy with peg-IFN and ribavirin. SVR rates following response guided therapy, were between eighty and eighty-one percent(260,261). Less favourable outcomes were demonstrated in individuals with genotype 1a infection with the Q80K mutation present at baseline testing. In this cohort, SVR rates decreased to between fifty-two and seventy-five percent (262). In phase III trials conducted in Japan, this treatment regimen produced even more successful results. This may be related to characteristics of participants included in the trials. Almost all included had genotype 1b infection and the Q80K mutation is much less prevalent in this strain of infection. Furthermore, participants selected for inclusion were non-cirrhotic (263).

Simeprevir was also licensed for use in individuals with genotype 4 infection, a trial of both TN and TE patients, with a primary end point of SVR twelve weeks following completion of therapy (SVR 12), demonstrated an overall SVR rate of eighty-three percent Sub-group analysis of the TE cohort revealed less favourable SVR rates of forty, sixty and eighty-six percent in prior null-responders, prior partial responders and prior relapsers respectively (264).

For individuals with genotypes 1 and 4, sofosbuvir was available for use in combination with peg-IFN and ribavirin. In the single-group, open-label study NEUTRINO, sofosbuvir was used in combination with peg-IFN and ribavirin in 327 patients infected with HCV genotypes 1, 4, 5, and 6. SVR 12 was achieved in ninety percent of the trial population, with no significant difference observed between genotypes; ninety-two, eighty-two, and ninety-six percent for genotypes 1a, 1b and 4 respectively. A reduction in SVR12 was observed in the presence of cirrhosis; eighty percent compared to ninety-two percent in the non-cirrhotic cohort, however the authors noted that at the time of its development and use, this treatment regimen still had the highest efficacy of any on the market for patients with cirrhosis (265).

The phase III, multicentre, randomised, open-label trial ION-1 used sofosbuvir and ledipasvir without peg-IFN. The trial assessed the impact of varying the duration of therapy as well as the addition of ribavirin on treatment outcomes. The genotype 1 TN cohort received fixed dose ledipasvir and sofosbuvir administered once daily and were then randomised to four treatment arms in order to investigate the trial objectives. The treatment arms were: ledipasvir/sofosbuvir for twelve weeks, ledipasvir/sofosbuvir plus ribavirin for twelve weeks,

ledipasvir/sofosbuvir for twenty-four weeks, ledipasvir/sofosbuvir plus ribavirin for twenty-four weeks. SVR rates among the four cohorts varied between ninety-seven to ninety-nine percent with no superior outcomes identified either by the addition of ribavirin, or prolongation of treatment duration (9).

The same trial design was conducted in a cohort of TE individuals, with randomisation stratified according to genotype (1a versus 1b), the presence or absence of cirrhosis and response to prior therapy; relapse or virologic breakthrough versus null response(266). SVR12 rates in individuals receiving twelve weeks of therapy, with or without ribavirin were ninety-six and ninety-four percent respectively and ninety-nine percent in those receiving twenty-four weeks of therapy. The presence of cirrhosis did impact on SVR rates with different durations of therapy. In the cirrhotic cohort, the overall SVR 12 was ninety-two percent, however a reduction was identified in the cohort assigned to twelve weeks of treatment, SVR 12 was eighty-six percent without and eighty-two percent with ribavirin. In the non-cirrhotic cohort SVR rates were ninety-five percent and one hundred percent respectively. In individuals receiving twenty-four weeks of treatment, response rates were similar irrespective of cirrhosis status. The authors concluded that extending the duration of therapy from twelve to twenty-four weeks in the presence of cirrhosis had a statistically significant superior effect, p=0.007 (266). Subsequent results from the phase III ION-3 trial suggested that TN, non-cirrhotic patients could be treated with an even shorter course of sofosbuvir and ledipasvir for eight weeks with no inferior outcomes in terms of SVR12 rates (10).

The combination of sofosbuvir with daclatasvir was also available for use in individuals with genotypes 1 and 4 disease that were deemed interferon intolerant. In the open label phase II trial AI444040, 126 TN and 41 TE genotype 1 participants were randomly assigned to receive one of the following treatment regimens: one week of sofosbuvir 'lead in' followed by daclatasvir and sofosbuvir for twenty-three weeks, daclatasvir and sofosbuvir for twenty-four weeks, or daclatasvir, sofosbuvir, plus ribavirin for twenty-four weeks (267). Overall SVR12 rates of ninety-eight percent were observed in the genotype 1 cohorts, with no superior effect observed in the setting of ribavirin therapy (267).

The phase IIb trial COSMOS examined SVR 12 rates in both TN and TE patients with genotype 1 disease treated with sofosbuvir plus simeprevir with or without ribavirin for either twelve or twenty-four weeks (268). One cohort consisted of previous treatment non-responders with no evidence of cirrhosis, and a second cohort consisted of a combination of both TN and TE patients with evidence of advanced fibrosis/cirrhosis. The primary end point of the trial was

SVR12. Overall SVR12 using this combination of therapy was ninety-two percent; ninety percent in the TE cohort and ninety-four percent in individuals with advanced fibrosis (268).

1.4.7.8.2 Genotypes 2 and 3

During HepFree, sofosbuvir was licensed for use in combination with peg-IFN and ribavirin in individuals infected with genotypes 2 and 3 HCV that had previously failed therapy (TE). LONESTAR-2, a small phase IIb trial demonstrated SVR rates of 96% in TE genotype 2 participants receiving twelve weeks of therapy, and 83% in the genotype 3 cohort(11). SVR rates were not influenced by the presence of cirrhosis, however the study population was small and so findings had to be interpreted with caution (11).

The phase III FISSION trial examined the efficacy of interferon free therapy, Here, cirrhotic and non-cirrhotic TN individuals with genotype 2 and 3 disease were treated with twelve weeks of sofosbuvir in combination with ribavirin (265). Treatment outcomes on this combination of therapy were non-inferior compared to outcomes following twenty-four weeks of the traditional combination regimen including peg-IFN and ribavirin, with SVR12 rates of 67% in both groups. The SVR rates in genotype 2 participants included in this trial were far superior compared to genotype 3; 97%, and 56% respectively (265).

FUSION investigated the efficacy of this treatment regimen in TE individuals that had not previously responded to an interferon-containing regimen. FUSION was a blinded, active-control study and approximately 30% of individuals enrolled had evidence of compensated cirrhosis at the time of screening for recruitment. SVR rates in genotype 2 participants enrolled were 86% and 94% for treatment durations of twelve and sixteen weeks respectively, and 30% and 62% in genotype 3 (269).

Given that genotype 3 appeared to be the more resistant virus, in VALENCE, an un-blinded phase III trial, the duration of treatment with sofosbuvir and ribavirin in both TN and TE genotype 3 patients was increased to twenty-four weeks, with improved SVR rates of 91% in the cohort without evidence of cirrhosis and 68% in those with cirrhosis (270). In all trials, excellent SVR rates were observed in genotype 2 cohort (269–271).

In the interferon-free trials described above, an inferior response to treatment was observed in individuals with genotype 3 disease. Results from the small phase II LONESTAR-2 trial suggested that sofosbuvir in combination with Peg-IFN and ribavirin was an effective regimen for use in genotype 3 infected individuals and therefore a large phase III trial was conducted to compare the efficacy and safety of sofosbuvir in combination with ribavirin, with and without peg-IFN in TE cirrhotic patients with genotype 2 HCV and in TN and TE patients with genotype 3 HCV (272). The multicentre, phase III open-label trial BOSON randomised patients in a 1:1:1 ratio to one of the three following treatment regimens: sofosbuvir with ribavirin for 16 weeks, sofosbuvir with ribavirin for 24 weeks, or sofosbuvir with ribavirin and peg-IFN for 12 weeks (272). The primary efficacy end point was SVR 12. The trial recruited predominantly genotype 3 patients; 92% versus 8% genotype 2. Baseline characteristics were similar to previous trials, predominantly white males of which 31% of all genotype 3 and 32% of genotype 2 participants had compensated cirrhosis (272). SVR 12 rates were similar across all treatment groups; 87% in the 16 week sofosbuvir and ribavirin cohort, 100% in the 24 week sofosbuvir and ribavirin treatment group and 94% in the group receiving sofosbuvir and ribavirin in combination with peg-IFN (272). In the genotype 3 cohort, SVR 12 rates were 71% in the 16 week treatment arm, 84% in the 24 week treatment arm and 93% in the peg-IFN arm and this was statistically superior. Virologic relapse rates were also lower in the peg-IFN cohort compared to the two groups receiving sofosbuvir and ribavirin; 5% versus 28% and 13% in the 16 and 24 week treatment groups respectively (272). Results from the BOSON trial provided clear evidence that in individuals with no contraindications to peg-IFN, a regimen consisting of sofosbuvir, ribavirin and Peg-IFN provided a promising option for treatment in genotype 3 infected individuals.

1.4.7.8.3 Real-world data

Trials that assessed SVR12 outcomes in both interferon-containing and interferon-free DAA HCV regimens produced very promising results. These results may have solely been due to the efficacy of the combination of agents used, but may have been influenced by a combination of factors including the controlled environment in which medical trials are performed and the characteristics of the individuals selected to participate. Trial participants, in addition to being both motivated and engaged are often less complex in terms of both their physical and psychological health needs. Therefore real-world outcomes observed when using the same regimens are often inferior to trial outcomes. A good example of this is the comparison between trial outcomes and real-world outcomes for individuals with genotype 1 HCV treated with telaprevir and boceprevir. Real-world outcomes were complicated by significant rates of premature treatment discontinuation due to the side-effect profile of the first generation PIs and SVR rates as a result were lower (273).

HCV-Target, a multicentre prospective observational study was performed to evaluate treatment outcomes in individuals with genotype 1 HCV treated with ledipasvir and sofosbuvir with or without ribavirin. The trial was conducted by the Hepatitis C Therapeutic Registry and Research Network. In the trial 154 individuals received eight weeks of therapy and 527 received twelve weeks, both without ribavirin. Treatment regimens were selected by the responsible clinician and therapy was administered in accordance with local protocols(274).A second study obtained data for analysis through Trio's Health Innovation Platform (275).Data was collected from 895 TN, non-cirrhotic patients with genotype 1 HCV that were treated with ledipasvir and sofosbuvir for either eight or twelve weeks. SVR was determined by intention to treat (ITT) analysis (276).

In both trials, SVR rates exceeded 94% across all sub-groups, with little difference identified between response rates in genotype 1a versus 1b and between the eight and twelve week regimens. The SVR rates observed were consistent with outcomes observed in the ION-1 and ION-3 trials. Furthermore, the real-world studies demonstrated low rates of discontinuation as a result of adverse effects, re-emphasising both the safety and tolerability profiles of DAAs (277). One limitation in using these studies as real-world data for comparison is that the participants included did not have cirrhosis nor any of the associated complex medical problems, therefore SVR rates demonstrated here may still be higher than would be expected when clinicians start to treat complex individuals that have previously been deemed either unsuitable for, or who have failed therapy with interferon-containing regimens.

Welzel et al assessed the safety and effectiveness of daclatasvir in combination with sofosbuvir with or without ribavirin in a large real-world cohort of individuals diagnosed with advanced liver disease. Criteria for inclusion included adults with HCV and a high risk of either decompensation or death within twelve months, with treatment carried out as part of a European compassionate use programme (278). The regimen recommended for use was daclatasvir and sofosbuvir for twenty-four weeks, with the addition of ribavirin at the discretion of the responsible clinician. The primary outcome measured was SVR12. In this study, eighty percent of participants recruited had liver cirrhosis, forty-six percent with a Model of End-Stage Liver Disease (MELD) score of more than ten. The majority of individuals recruited were TE, and unsurprisingly the most prevalent genotypes were 1 and 3, thirty-nine percent and twenty-one percent of the study population respectively (278). Ribavirin was used in three quarters of cases. The ITT SVR rate in the study population was in excess of ninety percent. On-treatment deaths occurred in two percent of the study population and a further four percent died during the period of follow-up. Given the severity of liver disease required to meet the inclusion criteria, these outcomes were probably not to be unexpected and may not have occurred as a direct consequence of the treatment administered in the trial(273). The authors concluded that treatment with daclatasvir and sofosbuvir was well tolerated even in individuals with advanced liver disease and high SVRs were achievable in these populations (278).

An expanded early access programme (EAP) was also available through NHS England for individuals with HCV of all genotypes that were at significant risk of death or irreversible damage within twelve months as a result of hepatic or extra-hepatic manifestations of HCV. Clinicians had the choice to treat eligible patients with sofosbuvir in combination with either ledipasvir or daclatasvir, with or without the addition of ribavirin for a fixed duration of twelve weeks. Individuals that fulfilled the criteria of the EAP were enrolled into the UK hepatitis registry, HCV research UK. A paper by Foster et al examined whether antiviral therapy was beneficial in unselected patients of all HCV genotypes with decompensation compared to individuals with equivalent stage disease enrolled into the same registry for at least six months prior to the start of the EAP. Through EAP, 480 patients received antiviral therapy and data was available on 467. Those treated had advanced liver disease; eighty-eight percent of cases had decompensated cirrhosis and/or a Childs-Pugh score was more than seven and nine percent of patients had previously undergone liver transplant for HCV with evidence of aggressive recurrence in the graft (279). Similar to the study by Welzel et al, the majority of individuals enrolled were male, Caucasian and were TE (279). The spread of genotypes treated were fairly equal, 54.6% versus 45.4%.

Analysis of the data identified a predilection for treatment with sofosbuvir and ledipasvir in the genotype 1 cohort and for daclatasvir with sofosbuvir in the genotype 3 cohort. In ninety-one percent of cases, ribavirin was added to treatment regimens. In 10.9% of cases viral response was followed by a subsequent relapse, 0.43% had no response to antiviral therapy, 3.6% died and a further 3.4% were lost to follow up. Large variations were seen in SVR rates between genotypes. SVR 12 in genotype 1 participants was 90.5% compared to 68.8% in genotype 3, $p<0.0001$. In terms of the safety profile and tolerability of DAAs in this complex group of individuals, treatment was discontinued prematurely in 5.6% of cases, and 7 patients died whilst on treatment (279). An improvement in MELD was identified in the cohort receiving antiviral therapy, when compared to the untreated cohort. In addition to this, rates of new episodes of decompensation were significantly reduced in the treatment cohort. No significant differences were observed in either episodes of sepsis, the development of HCC, or deaths between the treated and untreated cohorts (279).

1.4.8 Liver transplantation in hepatitis C

Worldwide, cirrhosis secondary to chronic HCV is the most common indication for liver transplantation (OLTx) (280). Graft re-infection has been documented in all cases of OLTx performed in RNA positive recipients (281). Fibrosis progression in the graft occurs at an accelerated rate compared to in the native organ with cirrhosis present in up to one third of transplant recipients at five years (282). Multiple factors including high VL pre and early in the post-transplant course, advancing donor age, prolonged ischaemic time, co-infection with cytomegalovirus and/or HIV, in addition to aggressive post-transplant immunosuppression may all contribute to rapid progression of fibrosis (283). Fibrosing cholestatic hepatitis (FCH) occurs in approximately ten percent of individuals that are transplanted with chronic HCV. FCH causes rapid liver dysfunction resulting in graft loss, usually within two years of the transplant (284).

1.4.9 Chronic hepatitis C virus infection in England: past and present

In England, the number of deaths attributed to HCV has quadrupled and the number of registrations for OLTx due to HCV related cirrhosis has increased nearly threefold between 1996 and 2014 (285). In 2002, in response to the growing burden of disease associated with HCV, a government publication was produced, aimed at intensifying actions with regards to the prevention of spread of the disease, the diagnosis of and subsequent treatment of HCV in

high-risk populations (286). HCV testing facilities were set up in genitourinary medicine (GUM) clinics, GP surgeries, prisons and in drug treatment centres. A pilot scheme was launched in prisons that distributed both disinfectant tablets and injecting equipment with clean needles to IVDUs. A public awareness raising campaign, 'faCe it' was developed by the Department of Health and education booklets were distributed to all general practitioners. Despite these interventions, results from a survey completed by primary care clinicians in London in 2003 demonstrated that knowledge surrounding HCV, in particular risk factors for acquiring the virus, diagnosis and management principles remained very low (287). In a later review of implementation of HCV services in 2008 it was identified that only one-third of primary care trusts had adopted, and were following the HCV action plan and fifteen percent of primary care trusts had failed to adopt the plan at all (288). Awareness of viral hepatitis is improving though. The 2015 Public Health England report on HCV in the UK demonstrated an increase in both awareness of, and testing and diagnosis of HCV in high-risk populations(285). There was a five-fold increase in the number of laboratory confirmed reports of HCV between 1996-2014 and a twenty-one percent increase in testing in primary care between 2012-2014 (285). Sentinel surveillance data has indicated an increase in testing in black and ethnic minority groups in particular in Asian ethnicity groups (285). An increase in testing in these other high-risk populations has been attributed to targeted awareness-raising campaigns in migrant communities. The prevalence of disease in the south Asian and eastern European populations from the sentinel surveillance data was reported as two percent and five percent respectively, highlighting the significant burden of disease in these groups and emphasising the need for focused case-finding programmes to be developed and implemented.

1.4.10 Screening programmes for chronic HCV

Primary prevention of HCV concentrates on activities aimed at reducing or eliminating the potential risk of transmission of the virus. Secondary preventative measures predominantly focus on developing and implementing screening programmes to identify infected individuals in order to reduce the potential burden of chronic disease.

When screening for any disease is considered, general principles that need to be evaluated include whether the disease in question poses an important public health problem, whether the natural history of the disease is understood, whether there is a latent stage of infection and finally whether effective treatments are available for use (289). The case for widespread screening for HCV is an area with contrasting views and opinions.

Historically, HCV screening was recommended for all individuals at an increased risk of infection; therefore anybody that had been exposed to the virus. The Centers for Disease Control (CDC) recommended screening in the following groups of individuals: anybody who originated from a country where HCV was endemic, PWIDs, individuals in receipt of a blood transfusion prior to 1992 and individuals requiring renal replacement therapy (290).

In 2012, guidance was modified to include one-time screening for anyone born between 1945-1965 because it was recognised that the highest burden of disease was concentrated in this age group (291). This change in screening policy has not been fully supported. There are several arguments discouraging the notion of widespread screening for HCV. One argument is that there is insufficient evidence available to support the progression of chronic HCV to end-stage liver disease (292).

In a review of screening recommendations, authors questioned the appropriateness of screening given that there is a paucity of data available to fully explain the natural history of, and therefore progression of fibrosis in HCV. Koretz et al proposed that in order to establish whether there are clear benefits to screening and subsequently treating HCV, a prospective study be conducted in order to document fibrosis progression from the point of infection (292). Although ideal in its approach, this prospective study would be difficult, if not impossible to perform given the previously discussed asymptomatic nature of acute HCV infection. In the literature, it is generally accepted that the incidence of cirrhosis 25-30 years

after infection with HCV ranges from between fifteen to thirty-five percent (293). Duration of virus exposure and resulting chronic liver disease is supported by the high cirrhosis-mortality rates observed in middle aged men and women living in Egypt (294). As previously discussed, there are few studies available to establish whether a relationship exists between duration of infection and progression of fibrosis due to a paucity of data in individuals with both a known duration of infection and paired liver biopsies for histological assessment.

In studies that have been performed to investigate the natural history of fibrosis in HCV, samples collected for histological analysis have often been obtained from individuals that have presented with symptoms prompting investigation. There is a lack of data available to evaluate progression of fibrosis in individuals with asymptomatic disease. There is therefore an element of selection bias in studies that have been conducted with the primary aim of investigating fibrosis progression and the natural history of HCV.

Data collected from individuals recruited to the HepFree trial will attempt to increase the understanding of fibrosis progression in asymptomatic cohorts of individuals infected with chronic HCV. In HepFree, data on fibrosis stage has been collected using a combination of both non-invasive and invasive techniques in all individuals with a positive test for HCV. This unique dataset will contain fibrosis scores for individuals that were tested and diagnosed with HCV through targeted testing in a population deemed as 'at-risk', implying a healthier cohort of individuals. As with pre-existing fibrosis progression studies, the major limitation of the HepFree data set is the unknown duration of infection. However because the programme targets individuals born outside of the UK, in most cases we assume that the virus was acquired in the first few years of life.

In the review of widespread HCV screening, Koretz et al stated that in the majority of cases of chronic infection with HCV, individuals remain asymptomatic and do not die from liver-related complications. If this was the case, they speculated that in addition to the costs associated with screening, diagnosis and treatment, risks associated with antiviral therapy outweigh any benefit derived from viral eradication (292). Reduction in QOL in individuals infected with chronic HCV and subsequent improvements following SVR have previously been discussed and disagree with Koretz et al. Evidence also exists that suggests higher mortality rates from both hepatic and extra-hepatic complications in anti-HCV seropositive patients compared with anti-HCV seronegative individuals even in the absence of end-stage liver disease (179,295). As discussed, HCV treatment has evolved from interferon monotherapy with poor

SVR rates and multiple side-effects to an era of interferon free all–oral DAA regimens. The vast improvement in SVR rates observed with new safe to use and easily tolerated agents support case finding initiatives.

In both Canada and the USA, cost analyses of screening programmes have been conducted (296,297). These studies considered both the cost of HCV treatment using both traditional and novel therapies together with costs associated with HCV related deaths and quality adjusted life years. In each of these analyses, screening was shown to be cost effective (296,297).

Currently, EASL and the National Institute for Clinical Excellence (NICE) recommend targeted HCV screening in the following groups of individuals (298,299)

- PWIDs or individuals with a past history of injecting drug use.
- Individuals in receipt of a blood transfusion prior to 1991 or blood products prior to 1986.
- Migrants originating from a country with a prevalence of viral hepatitis of more than two percent.
- Children born to mothers infected with HCV.
- Prisoners and young offenders.
- Looked-after children and young people in care homes.
- The homeless and people living in hostels.
- HIV positive men who practice sex with men.
- Close contacts of a known HCV carrier.

1.4.10.1 Screening for viral hepatitis in PWID

Drug policies in England recognise the need for a harm reduction approach in PWIDs. This approach is facilitated by the provision of opioid substitution programmes, key worker support in substance misuse centres, needle and syringe programmes as well as information available on the transmission of blood borne viruses (BBVs). Guidance exists recommending screening in all service users accessing drug services. Screening in this population can be performed either by venepuncture or alternative testing methods including dry blood spot (DBS) and mouth swabs in individuals with difficult venous access (298). Post screening, it is recommended that all service users be offered vaccination against HBV and annual HCV tests

in those with an on-going risk factors for infection (298). Opt-out testing for BBVs in prisons began in England in April 2014 following a National Partnership Agreement between the National Offender Management Service (NOMS), NHS England (NHSE) and Public Health England.

1.4.10.2 Screening in immigrant populations

Currently in the UK, testing for viral hepatitis in immigrant populations is the responsibility of healthcare professionals, namely those operating in primary care. Guidance recommends that testing is offered to all adults and children at increased risk of infection, in particular migrants originating from medium or high risk prevalence countries, at the point of registration with a new GP (298).

The prevalence of viral hepatitis in migrants residing in the UK is not known. Investigators have previously attempted to establish whether prevalence data from immigrants' countries of origin can be used to predict the prevalence of disease in migrants residing in host countries. Authors of HBV screening studies performed in Asian and Somali immigrants living in New York City and Minnesota concluded that disease prevalence in immigrants reflected the prevalence in their country of origin (7,8). This was not the case in HCV screening studies performed in immigrants from the former Soviet Union residing in New York and in south Asian immigrants living in England (300,301). One reason for the variation in findings may be the validity of prevalence data available for interpretation; epidemiological studies are expensive to perform and the results obtained are very dependent on the characteristics of the individuals recruited.

Outreach studies previously performed in migrant populations have demonstrated that case-finding for viral hepatitis in these populations is feasible (301–304). These studies employed both a variety of different invitation approaches and locations for testing. Events were advertised using posters and flyers placed in shops, barbers and community centres. In addition to the written adverts, religious leaders were approached and recruited to help to both increase the profile of hepatitis testing and to attempt to overcome barriers associated with screening.

There were several limitations associated with the methodology of the aforementioned studies. The first limitation relates to the methods used to invite individuals for testing. In these studies, viral hepatitis testing was only performed in individuals that self-presented in response to the advertising campaign. This method of recruitment could have potentially resulted in selection bias, with testing performed more frequently in individuals with higher levels of knowledge regarding viral hepatitis and the implications of chronic infection who self-selected themselves for screening. The second limitation relates to the locations selected to perform testing by the studies. Screening was predominantly performed in public areas; individuals may have had reservations about attending and participating in a public place such as a community centre if they perceived that this act may be witnessed and reported negatively within their community because of stigma associated with HCV.

1.4.10.3 Barriers to screening in immigrant populations

It is widely accepted that chronic viral hepatitis affects disproportionately high numbers of the most deprived and marginalised communities worldwide. In these populations, there are multiple barriers that prevent individuals from engaging with both screening for viral hepatitis as well as any subsequent assessment and treatment that may be required. In addition to obstacles in engaging these populations, it is clear that challenges also exist in engaging health professionals to promote and facilitate testing in these groups (287).

The success of a screening programme is dependent on how well the target population is engaged (305). Ideally for a population to be engaged, they would possess awareness, knowledge and understanding of the disease being screened for, in addition to knowledge about both the risks and implications of leaving the disease both unidentified and untreated in the long-term. Engagement by immigrant populations in viral hepatitis screening can be predicted to a certain extent by reviewing attendance data at pre-existing preventative screening programmes. Historically, both socio-economic deprivation and migrant status have been associated with non-engagement with pre-existing preventative care strategies (306,307). In England, research has demonstrated that attendance by migrant populations at breast, cervical and colorectal screening programmes is poor, in particular by groups of individuals originating from south Asia and the Indian subcontinent (308–310). Inaccurate screening registers, frequent changes of address by individuals and extended periods of overseas travel have all been implicated as reasons for poor attendance amongst migrant groups (308). In addition to these, language and communication barriers impact on both engagement in screening programmes as well as access to healthcare services on a larger scale (311,312).

Illiteracy is prevalent in migrant populations residing in England, with the highest rates observed in first generation immigrants, in females, and in individuals of advancing age (313). It has been estimated that more than half of all Bangladeshi and Pakistani women and nearly a quarter of men aged over fifty are illiterate in any language, and less than one third of women from these ethnic groups are able to read and understand English (313). In these populations, written invitations to participate in preventative screening strategies are particularly ineffective and the high rates of illiteracy in all languages prevent the use of translations (313). Another factor that might be associated with poor engagement in preventative care strategies by migrant populations is clinician-patient relationship. Research has identified that black and ethnic minority groups have a lower level of trust in their clinician compared to individuals of Caucasian origin (314,315). This lack of confidence in healthcare providers may impact on an individual's decision to participate in preventative care interventions offered to them (315,316).

Research conducted in America, Australia and the Netherlands has focussed specifically on the attitudes of migrants towards testing for viral hepatitis. Data from these studies augments pre-existing knowledge of the potential obstacles facing screening programmes (317–321). Key themes including low levels of awareness about viral hepatitis, little knowledge pertaining to the potential routes of transmission of the viruses, symptoms associated with the diseases and the long-term implications of chronic infection were identified (317–321). In this research, the insidious onset, as well as the asymptomatic nature of infection had a negative impact on individuals accepting the offer of testing. Absence of symptoms has previously been associated with reluctance to attend for, and participate in preventative care screening strategies (322). Stigma was also found to influence an individual's decision to participate in viral hepatitis testing. In developed countries, there is a well-established relationship between IVDU and a positive diagnosis of viral hepatitis, therefore an association exists between a viral hepatitis and socially unacceptable behaviours. Fear about how an individual might be perceived and subsequently treated by other members of their community if they are seen participating in testing might impact on their decision to engage with testing strategies (323). Interestingly however, in specific viral hepatitis studies by Coronado et al and Nguyen et al clinician recommendation for testing had a positive effect on subsequent engagement rates (324–326).

1.5 Objectives of the investigation

Through the HepFree trial and the associated sub-study, I aimed to explore the following:

1. The feasibility of utilising electronic records in primary care in order to identify immigrants at risk of viral hepatitis that would benefit from screening for viral hepatitis.
2. The acceptability of setting up a screening programme for viral hepatitis in primary care.
3. The preferred method for inviting first and second generation immigrants to attend for testing, specifically whether a targeted invitation letter has value when compared to a standard, generic invitation letter.
4. The demography and prevalence of viral hepatitis in first and second generation immigrants residing in culturally diverse area of England (Bradford).
5. Whether undiagnosed chronic HCV results in increased utilisation of healthcare resources in primary care.

In the following chapters I will describe the methods used to explore the above objectives, present and discuss the research findings, critique the methodology used by HepFree and make some recommendations for future research.

2. Materials and Methods

Within this chapter I will describe the methods used to conduct the HepFree trial including trial design, hypotheses, trial set up, participant identification, selection and invitation, participant enrolment and data collection. Statistical methods used for the exploratory analysis will also be discussed.

2.1 Trial design

HepFree is a cluster randomised controlled trial conducted in GP practices in four areas of England: north-east London, south-east London, Bradford and Oxford. The trial was designed to invite up to 48,000 eligible participants from fifty GPs that had been recruited to participate and subsequently randomised to the intervention arm of the trial. A further eight practices were recruited and assigned to the control arm of the trial. HepFree set out to examine and test the following hypotheses that were included in the protocol:

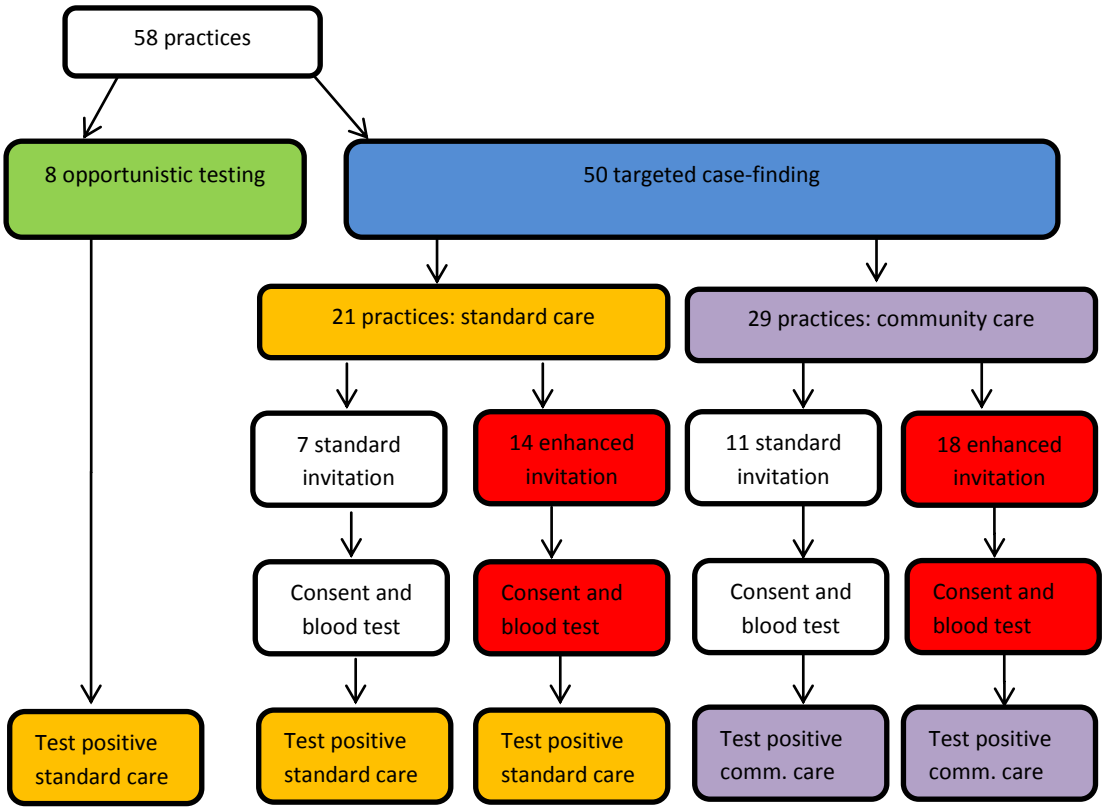
- That targeted case-finding for viral hepatitis in first and second generation immigrants in primary care is superior to opportunistic testing in identifying individuals with viral liver disease.
- That providing additional information on the condition of viral hepatitis encourages individuals to enroll in the study and take up the offer of a screening blood test.
- That providing treatment and follow-up for individuals who test positive for viral hepatitis in the community is superior, in terms of compliance and adherence to therapy, compared to treatment and follow up in secondary care (standard care).

The study included two nested interventions within the intervention arm. One intervention involved randomising practices to either community care or standard, hospital based care in the event of a positive diagnosis of hepatitis. The other investigated the hypothesis that an 'enhanced' invitation letter was more valuable than a 'standard' letter. The 'standard' letter invited the recipient to take part in a research project that aimed to establish the best way of identifying individuals infected with viral hepatitis from those who are deemed at risk, based on their own, or parents country of birth. The 'enhanced' invitation letter included an additional page of information on the viruses been tested for, the implications of chronic infection and reasons why the participant had been selected to participate in the trial. A copy of both invitation letters used in the trial are available in Appendix 3. From the fifty practices that were randomised to the targeted case-finding arms of the trial, twenty-one were assigned to standard care follow-up and twenty-nine to community care follow-up. Eighteen out of the fifty practices were assigned to the intervention arm that sent a simplified

'standard' invitation letter to all eligible participants, and the remaining thirty-two invited participants used the 'enhanced' trial invitation letter. The eight practices randomised and assigned to the control arm provided information on testing rates and subsequent engagement with treatment in a further 4,000 individuals. Trial randomisation was performed using the method of minimisation (Peacock & Simon, 1975). The programme managing allocations was web-based, and developed using Java at Queen Mary University London.

Although the broad principles are similar, there are differences between case finding (targeted testing) and screening. Case finding (or targeted testing) is a strategy used for targeting resources at individuals or a population based on the presence of risk factors. It involves performing a systematic search to identify the 'at- risk' population followed by an invitation to attend for testing, as opposed to waiting for individuals to present with signs and symptoms relating to the disease of interest. This is very similar to screening in that both processes risk stratify a population prior to further investigation. The primary purpose of screening is to detect early disease in large numbers of asymptomatic or 'healthy' individuals. There are several principles that must be fulfilled before a testing strategy can be adopted as a screening programme, these principles are referred to as Wilson's criteria.

Figure 4: The HepFree cluster randomised controlled trial design



A flow chart summarising the HepFree trial design. Comparing testing rates in GP surgeries performing targeted testing (coloured blue) with opportunistic testing in control practices (coloured green) will investigate whether targeted case-finding for viral hepatitis in first and second generation immigrants in primary care is superior to opportunistic testing in identifying patients with viral liver disease. Within the targeted case-finding arm (blue) there were two nested interventions; the first to investigate whether providing additional information on the condition of viral hepatitis encourages individuals to participate in testing, and the second to determine whether community based treatment improves compliance and engagement with treatment. Practices in the red boxes sent an enhanced invitation including an additional information sheet to their eligible population and practices in the white boxes sent a standard invitation letter. Participants with a positive test for viral hepatitis registered at a GPs assigned to the yellow boxes in the flow chart above were assessed and treated in hospital (standard of care) and participants with a positive test registered at GPs assigned to the purple boxes on the flow chart were assessed and treated in satellite hepatology clinics based in the community.

*At the time of enrollment into the trial, participants were blinded to their treatment location allocation in the event of a positive viral hepatitis test result. A second-stage consent was sought from all participants who had a positive test result at the time of their diagnostic assessment in secondary care. Once the second-stage consent had been obtained,

participants were un-blinded and informed of their treatment and monitoring allocation, either hospital treatment and follow-up, referred to as standard care or treatment and follow-up at a satellite clinic in the community. Any participant that withdrew consent for the second-stage of the trial was treated as per standard care. Treatment allocation was concealed until after the initial consent to participate in the trial had been obtained, in an effort to prevent bias from being created between recruitment in the two arms of the trial.

- Comparison of testing results in control and intervention practices; coloured green and blue respectively will investigate hypothesis one, that targeted case-finding for viral hepatitis in first and second generation immigrants in primary care is superior to opportunistic testing in identifying patients with viral liver disease.

- Comparison of case-finding outcomes in practices inviting eligible individuals using the enhanced invitation with outcomes in practices using the standard invitation letter; coloured red and white respectively on the flow diagram will investigate hypothesis two, that providing additional information on the condition of viral hepatitis encourages individuals to enroll in the study and take up the offer of a blood test.

- Comparison of the engagement and treatment outcomes in participants receiving standard of care versus care in the community; coloured orange and purple on the flow chart respectively will investigate hypothesis three, that providing treatment and follow-up in a community setting increases patient engagement, adherence and compliance with both appointments and therapy.

2.2 The HepFree Trial

2.2.1 The trial team

The HepFree trial team involved the CI, a dedicated trial manager in addition to a part-time data manager and statistician. This team was based in London and responsible for both the submission of the ethics application and initiation of the trial. The process of trial set up, which was conducted by the London team, is described below.

2.2.2 Trial set up

HepFree, following a grant application from Professor Foster, was funded by the NIHR through the Programme Grants for Applied Research. A copy of the trial protocol, written by the CI with support from the trial coordinator, is attached in Appendix 1. The trial was set up by the team in London prior to me joining the group in October 2013. Set-up involved several processes described below.

In order to apply for sponsorship from the Bart's Health NHS trust and Queen Mary University London, an Integrated Research Application System (IRAS) form for the trial was completed, and all documents submitted for internal peer review at the Blizard Institute, 4 Newark Street, London, City of London, E1 2AT and external review by the Bart's Health NHS Trust Research Development team, Joint Research Management Office, Queen Mary Innovation Centre, Lower Ground Floor, 5 Walden Street, London, E1 2EF. Once provisional sponsorship had been granted by the Joint Research Management Office for Bart's Health NHS Trust and Queen Mary University London, Mile End Road, London, E1 4NS, the trial documents were submitted for central ethics review to the National Research Ethics Service, HRA NRES Centre Manchester, Barlow House, 3rd Floor, 4Minshull Street, Manchester, M1 3DZ. Following central ethics approval, full sponsorship was provided by Queen Mary University London and at this point the CI site was able to distribute study specific information to the research teams at the local coordinating sites in Bradford, Oxford and south-east London.

2.2.3 Trial modifications

Modifications were made to the HepFree trial protocol once permissions had been granted and sites were being recruited and randomised. During randomisation, it was evident that practices had far larger numbers of potential study participants registered than had been predicted. This observation was related to changes in primary care whereby small, single handed practices were encouraged to merge to form larger collective practices. This would have had a negative effect on both the trial design and the study budget. The trial methodology was therefore amended and a 'cap' introduced. Practices that were recruited to the trial following the protocol amendment were instructed to invite only five hundred individuals at random from the list of all potential study participants registered in the practice.

This modification meant that the trial conducted participant recruitment using two different methods as described below. Practices either invited all potential study participants who were registered there, referred to as comprehensive enrolment, or they invited five hundred potential participants selected at random from the list of all potential study participants. The second method of recruitment was referred to as selective enrolment. Of the fifty practices recruited to perform targeted case-finding in London and Bradford, sixteen practices utilised the comprehensive enrolment methodology, and thirty-four performed selective enrolment. The methods used to pre-select participants are discussed within the section titled Participant Retrieval.

A second modification was made to the trial once sites had been opened and recruitment had commenced. Staff within the practices provided feedback to the trial team regarding the low response rates to the trial letter invitations that had been sent as well as historically low response rates observed in migrant populations to written invitations for other established screening programmes. In response to this, a further amendment was made to the trial protocol that allowed members of staff to approach potential study participants that attended the practice for another clinical reason to offer the viral hepatitis test. This method of recruitment was referred to as opportunistic testing. Within the amendment, the trial team was given permission to design and activate an electronic alert on the clinical computer systems in the practices. The alert, once created, was linked to the trial report that contained a list of all potential study participants. From this point, whenever the electronic medical record of an eligible individual was retrieved by a member of staff within the practice (receptionist, healthcare assistant, practice nurse, clinician) a pop-up alert appeared on the home page of the record prompting them to enquire as to whether the individual would like to participate in the trial. If the individual did wish to participate following the verbal prompt, a copy of the patient information sheet (PIS) both in English and in their native language, if available, was provided and the individual was given the opportunity to read it prior to undergoing testing, which occurred either on the same day or at a future appointment arranged by the practice.

2.3 Trial methodology

2.3.1 The control arm

Practices randomised to the control arm of the trial received detailed written information pertaining to the trial aims, objectives and methods. This was delivered in the form of the research protocol which was included as part of the trial site file. The control practices received a single face to face meeting with the clinical fellow working on the HepFree research team, known as the site initiation visit (SIV), during which the trial aims, objectives and methodology were discussed. The SIV was attended by general practitioners, the practice manager, practice nurse and healthcare assistants. In the meeting, the clinical fellow delivered an education session on viral hepatitis that included indications for testing and consequences of long term infection. The education session was delivered with the aid of a power-point presentation and all in attendance received a handout of the slides. Throughout the presentation, members of staff present were encouraged to ask questions. A copy of the handout provided at the teaching session is included in Appendix 2.The purpose of the education session was to encourage practitioners to offer testing to individuals considered at risk of viral hepatitis, individuals who would have been eligible if the practice had been randomised to perform targeted case-finding. Clinicians were encouraged to consider offering the viral hepatitis blood test to eligible individuals who attended the practice for either a consultation, or when registering as a new patient. The purpose of this was for the trial to be able to assess the impact of education on subsequent opportunistic case-finding for viral hepatitis in 'high-risk' individuals.

2.3.2 The targeted case-finding (intervention) arms

In practices assigned to perform targeted screening, potential study participants were invited to attend for screening using one of the two trial invitation letters, depending on the outcome of randomisation. The trial invitation letters are included in Appendix 3. The invitation letter provided each individual with the opportunity to attend their practice to consent to participate in the trial, and undergo a viral hepatitis screening test. During the SIV for targeted screening practices, members of staff received the same education session that was provided to control practices, as well as teaching on additional techniques and processes required to conduct the trial.

Administrative staff were taught how to generate and distribute personalised screening invitation letters using the clinical computer system within the practice. Allied healthcare professionals were taught how to obtain consent, perform blood sampling for analysis, complete the sample request form, and how to locate and complete the trial specific template that had been published on the electronic records system used by the practice. Finally staff were taught to input Read codes denoting the results of the screening blood tests on to each participants electronic medical record and instructions were given on how to refer a participant to the HepFree trial team (myself for Bradford patients) in the event of a positive screening test result.

In targeted screening practices, successful enrollment into the trial involved asking the trial participant to read, understand, and sign an up-to-date version of the consent form; copies of the patient information sheet and consent form are in Appendices 4 and 5. Once consent had been obtained, six millilitres of venous blood was obtained by venepuncture and sent in a Serum Clot Activator VACUETTE® sample tube with a study specific proforma requesting for the sample to be tested for HBsAg and anti-HCV to the local virology laboratory. For Bradford the selected laboratory was The Old Medical School, Leeds General Infirmary, Thorseby Place, Leeds, West Yorkshire, LS1 3EX. A contract was set up and agreed between the official sponsor of the trial Queen Mary University, Whitechapel, London, E1 2AN and the Leeds Teaching Hospitals NHS Trust for processing and reporting of trial blood samples. To facilitate identification of study samples I created a study specific sample request proforma, available in Appendix 6.

Practice payment

Practices received monetary incentives for trial related activities. For time taken to set up the trial and to produce a data extract, control practices received £250 from the HepFree trial budget. In practices performing targeted screening, as the trial has been adopted by the NIHR Clinical Research Network (CRN) portfolio, financial support was provided by them. Table 4 summarises the payments made to targeted screening practices for trial related activities in Bradford.

Table 4: HepFree study support costs

Study support costs paid to targeted testing practices participating in the HepFree trial by the Clinical Research Network

Trial related activity	**Cost (pound sterling)**
Set up costs	475.28
GP check on participant list for suitability	160.00
Reminder set up	12.44
Text Message reminder service set up	11.00
Consent and Screening	7.32
Book appointments (per appointment)	2.07
Invites (per invite)	0.41
Exclusions Nurse	0.37
Text message reminder (per SMS)	0.15

2.4 HepFree trial inclusion criteria

Potential study participants included anyone registered within one of the designated targeted screening practices that:

- Originated from a country with a prevalence of viral hepatitis of more than 2% (List of countries available in Appendix7).
- Had a parent who originated from a country with a prevalence of viral hepatitis of more than 2%
- Was eighteen years of age or older.
- Had capacity to consent to participate.
- Had no documented evidence of previous viral hepatitis screening within the last five years.
- Did not have a pre-existing diagnosis of viral hepatitis.

Due to uncertainty surrounding whether subjects had historically been screened for HBV infection prior to immunisation, we did not exclude anyone that had previously been involved in a HBV immunisation programme.

2.5 The HepFree trial in Bradford

I joined the HepFree trial team in October 2013. Once full sponsorship for the trial had been granted in London, my first role was to set up Bradford as a coordinating trial site. In order to do this, I facilitated the development and implementation of a contract between Barts Health NHS Trust, The Royal London Hospital, Whitechapel, London E1 1BB and Bradford Teaching Hospitals NHS Foundation Trust, Bradford Royal Infirmary, Duckworth Lane, Bradford, BD9 6RJ. Once the contract had been finalised, site feasibility was completed and an agreement produced between the Research Development team at Bradford Teaching Hospitals and the Research Management Group at the Bradford District Care NHS Foundation Trust to enable the screening trial to be performed in GPs in the community. The trial approval letters are available in Appendix 8.

Prior to commencing recruitment of sites in Bradford where the trial would be conducted, I had to establish the methods that would be used to interrogate primary care clinical computer systems in order to identify potential study participants. Moreover, I had to establish the methods that we would use to collect both demographic and disease status data on participants that consented to, and participated in the screening trial. As described within Participant Retrieval, the trial team had decided to identify potential study participants, also known as eligible individuals to participate in screening based on pre-existing demographic data stored in the form of Read codes, within their electronic medical records. These 'Read code searches' were initially established in London for use on GP electronic records stored in the EMIS web system. In Bradford an alternative system, SystmOne (S1) was used. I was responsible for designing and creating the specific reports used to identify and record data from potential study participants in Bradford.

In order to establish the Read codes to be included in the trial reports, also referred to as 'eligibility reports', I applied for a research passport. This allowed me to gain access to a S1unit in a GP surgery in Bradford. Here, I interrogated the clinical coding catalogue that is published and available for use by members of staff that code clinical information in patient records. Interrogation consisted of performing multiple searches using different Read codes pertaining to ethnicity, country of birth, and main spoken language in order to understand how best to identify individuals who were already registered within the practice. As well as designing and running reports using Read codes, I performed surname analysis to identify participants who were likely to belong to particular ethnic groups of interest to the trial. I then accessed and reviewed the Read codes used in the patient demographic section of the S1 record to gain a better understanding about the way in which practices use Read codes to store demographic data relating to ethnicity, country of birth and main spoken language.

Once I was satisfied with the list of Read codes that I had acquired from my preliminary searches on S1 that would be used in the eligibility reports for the trial, I arranged a meeting with the data quality team at the Yorkshire and Humber Commissioning Support Unit, formerly The West and South Yorkshire and Bassetlaw Commissioning Support Unit, West Yorkshire Office, Douglas Mill, Bowling Old Lane, Bradford, West Yorkshire, BD5 7JR. Here, with the help of one of the members of the data quality team, I devised and built the eligibility reports that were published on S1 for use by practices that we recruited to HepFree.

Once the eligibility searches had been published on S1, I began the process of practice recruitment. Recruitment, site initiation, training and all support required by practices during the period of screening were performed solely by me in Bradford.

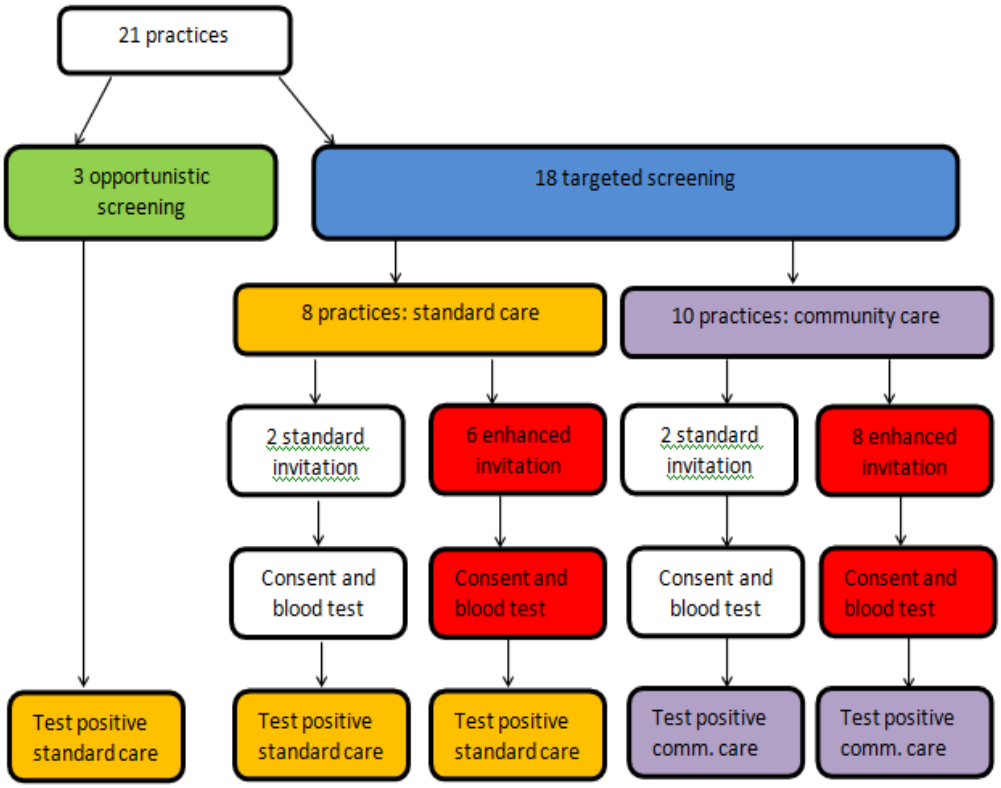
Once practices had been recruited, opened and screening had commenced, all participants with a positive hepatitis screening test were assessed, clinically managed and followed-up by the trial team, either in secondary care or in the community, depending on the randomisation outcome of the practice at which they were registered. In Bradford, I arranged and conducted all assessments and follow-up appointments for participants with a positive screening test. In addition to this I also captured and entered all trial related data in the trial eCRF, a form I had assisted in the development and testing of, alongside the clinical fellow and data manager in London.

In the following sections I discuss in detail the methods of practice selection and recruitment, the study specific training that was delivered to practices at the time of the site initiation and the methodology of participant retrieval. Finally I discuss the exploratory analysis methodology.

2.5.1 Practice selection and recruitment

Twenty-one GPs were recruited from two Clinical Commissioning Groups (CCG); Bradford City and Bradford District. Eighteen practices were randomised to the targeted screening arms and three to the control arm of the trial. Within the targeted screening practices, ten were allocated to comprehensive enrolment and eight to selective enrolment. Data from the ten practices performing comprehensive enrolment were included in the exploratory analysis. The distribution of the practices is illustrated below.

Figure 5: The HepFree trial design in Bradford



A flow chart summarising the numbers of practices randomised to each arm of the HepFree trial in Bradford. Comparing testing rates in GP surgeries performing targeted testing (coloured blue) with opportunistic testing in control practices (coloured green) will investigate whether targeted case-finding for viral hepatitis in first and second generation immigrants in primary care is superior to opportunistic testing in identifying patients with viral liver disease. Within the targeted case-finding arm (blue) there were two nested interventions; the first to investigate whether providing additional information on the condition of viral hepatitis encourages individuals to participate in testing, and the second to determine whether community based treatment improves compliance and engagement with treatment. Practices in the red boxes sent an enhanced invitation including an additional information sheet to their eligible population and practices in the white boxes sent a standard invitation letter. Participants with a positive test for viral hepatitis registered at a GPs assigned to the yellow boxes in the flow chart above were assessed and treated in hospital (standard of care) and participants with a positive test registered at GPs assigned to the purple boxes on the flow chart were assessed and treated in satellite hepatology clinics based in the community.

Practice recruitment

In order to increase awareness of the trial and assess clinician interest, two meetings were arranged by the research team in Bradford for general practitioners and practice managers. The meetings were hosted by a consultant hepatologist, two research nurses and theHepFree trial manager who visited from London. The meetings were advertised both in the CCG

newsletter and in an electronic mail (email) that was sent to all clinicians by a central coordinator at the CCG. At the meeting, contact details were taken for all clinicians who expressed an interest in participating in the trial, and these practices were prioritised when trial recruitment began in January 2014.

In Bradford I was responsible for recruiting all practices to participate in the trial. Practices that had expressed an interest in participating in the trial at the time of the HepFree meetings were prioritised and contacted in the first wave of recruitment. Once this list had been exhausted, a list of GPs in both the Bradford City and Bradford District CCG was accessed from the internet. The terms 'Bradford City CCG' and 'Bradford District CCG' were entered into the internet search engine Google to access the following websites: www.bradfordcityccg.nhs.uk and www.bradforddistrictccg.nhs.uk. From the homepages of the websites there was a link for 'Your services'. On this page there was a list of all GP practices within the CCG with addresses and telephone numbers. From this list, I contacted practices, prioritising them based on their geographical location and ethnicity data available from the census, offering trial places to practices within the postcode districts BD7, BD8 and BD9 first as these areas had high ethnic diversity.

Initial contact with practices was made by a telephone call to the practice manager in which the trial aims, objectives, and methods were discussed. The telephone call was followed up immediately with an email that provided a brief summary of the telephone discussion, a short trial synopsis and contact details of the trial team in Bradford, so a face to face meeting with myself and one of the hepatology research nurses at a mutually agreeable time could be requested. The face to face meeting, unlike the site initiation visit was not mandatory, but provided practices with the opportunity to meet the trial team prior to agreeing to participate if they wished, in addition to providing them with opportunity to discuss any issues related to the trial that might have arisen. At the face to face meeting if the practice decided that it would like to adopt the trial, the specific search that had been designed to identify potential study participants (also known as the participant eligibility search) was accessed and run on S1. If practices did not want to participate in the initial face to face meeting, then verbal instructions on how to locate and run the participant eligibility search were provided over the telephone. The number of potential study participants in the practice, data derived from the participant eligibility report was required in order for the practice to be randomised and entered into HepFree. Once this information was available, a randomization proforma was completed by myself, and submitted to the trial statistician via email. A copy of the

randomisation proforma is available in Appendix 9.Once the outcome of randomization was known, the practice was informed and a time arranged to conduct the SIV.

Due to the nature of how we were recruiting practices, there was no formal trial contact and initiation procedure, however all practices that failed to respond to the email that was sent to them following the first telephone call, or those that did not make contact with the trial team to disclose the outcome of their decision to participate in the trial within one week of the first telephone call were re-contacted by me. Practices were contacted either by email or telephone call, and this process was repeated at a frequency of at least once per week until an outcome regarding participation had been established. All practices that declined the invitation to participate in the trial when contacted were offered a face to face meeting with the research fellow (myself) to discuss any potential barriers that may have been preventing them from participating in the trial.

After four months of recruitment using the methods described above, a third meeting was organised by the hepatology research team in an attempt to improve engagement by clinicians in primary care with the trial. Again, this meeting was advertised, and the invitation extended to all clinicians, practice managers, and practice staff working in general practice within the two CCGs. Despite the third meeting, we were still not able to recruit the required number of practices for the cluster trial design and so a different approach was adopted. I set up and attended a meeting with the head of the CCG in order to discuss the trial aims and objectives as well as the difficulties we were encountering with recruitment of sites in primary care. The head of the CCG personally contacted all clinicians that they felt would be both willing, and able to incorporate the trial into their workload and run it efficiently. This email lead to the recruitment of two more practices, but this did not complete recruitment for Bradford and so recruitment via telephone and email strategy continued until the required number of practices had been recruited.

2.5.2 Trial specific training

Once the outcome of randomisation was known, the SIV was arranged by me, with the practice, in order to deliver the trial specific training required for the practice to be able to be opened for recruitment. At the SIV, the lead clinician in the practice, practice manager, practice nurse and/or healthcare assistant were in attendance. I conducted all SIVs with assistance from a member of the data quality team from the Commissioning Support Unit.

The data quality team member attended the meetings to provide training on the S1 data management system, discussed below.

As discussed previously, the visit started with an education session delivered by the clinical fellow (myself in Bradford) with the aid of a PowerPoint presentation. This session was delivered in an informal manner with time for discussion, and provided an overview of the current and projected burden of disease associated with viral hepatitis in addition to the aims and objectives of the trial, the trial design and methodology. There were also slides relating to good clinical practice, including data protection, consent, and reporting of adverse events. Of particular importance for practices randomised to the community arm of the trial, but also pertinent for all practices, cluster allocation bias was discussed by the clinical fellow and the lead clinician was asked to sign a contract, available in Appendix 10,that stated that they understood and agreed to avoid the introduction of bias related to treatment allocation.

2.5.3 Generating the trial invitation letter

As stated in the methodology, potential study participants were invited to participate in the trial using one of two invitation letters both of which are available in Appendix 3. Practices were advised to personalise the letter by adding their letter head to the top of the letter as well as their contact details in the body of the text that would provide the recipient with details to enable them to book an appointment for testing.

In order to generate an invitation letter populated with the study participant's details, the invitation letter template had to be uploaded onto S1. At the SIV the member of the data quality team taught the practices how to do this. In addition to generating the letter using S1 we asked the administrative staff to enter a specific Read code (9OT4) in the electronic medical record of each individual at the time when the letter was produced. This allowed the trial team to produce a report containing details about the date and time that each letter had generated by the practice for each participant.

Translations of the invitation letter were available in Bengali, Gujurati, Urdu, Polish, French and simplified Chinese. If the staff responsible for distributing the invitation letters were aware that the main spoken language of a potential study participant was one of the

languages listed above, they were encouraged to send this in addition to the English version of the invitation.

During this part of the training session, the data quality team also added the electronic alert to S1 and linked it to the list of potential study participants (the eligibility search). The electronic alert was the reminder that would appear each time the medical record of a potential study participant was retrieved by a member of staff in the practice, thereby enabling them to offer testing opportunistically. By linking the electronic alert to the list of potential study participants, the alert would only appear on the medical records of individuals that were eligible to participate in the trial.

2.5.4 Consent training

This session was delivered by the research fellow (myself) and covered the following principles: obtaining and recording consent, sending the blood sample for processing and completion of the study template. The PowerPoint presentation provided an introduction to consent, containing an overview of the principles of both capacity and consent. In this additional session, training was provided for the named members of staff within each practice that were responsible for taking consent, and included how to confirm participant eligibility, the methods involved in obtaining consent, instructions on how to fill the consent form and where to store each consent form. A laminated pre-filled consent template was provided to each practice to act as an 'aide memoire'. Training was also provided on how to complete the study specific blood request proforma and how to complete the trial template that was published and available for use on S1. The template will be discussed further in the section titled The Study Template.

2.5.5 Recording case-finding test results

Staff within each practice that were designated the task of reviewing all viral hepatitis test results were taught how to code each result in the electronic medical record of each participant. Members of staff were also instructed how to inform the trial team in the event of a positive test result. The results of all of the trial samples that were received and processed by the virology laboratory at Leeds General Infirmary were returned to the practice

for review by the lead clinicianonS1 using an electronic link. The clinician or other named member of staff then had the task of entering two Read codes into each electronic medical record. The purpose of this was to enable the research team to collect data on anonymised test results. The four Read codes available to the practice staff are summarised in Table 5.

Table 5: Read codes to document viral hepatitis test outcomes

Read codes available within SystmOne that were recommended by the trial for use to document the results of the viral hepatitis tests. Once a Read code was assigned to a test result, this anonymised data could be retrieved by the data team.

XaPEy	Hepatitis B screening test positive
XaPLp	Hepatitis B screening test negative
XaPLI	Hepatitis C screening test positive
XaPLZ	Hepatitis C screening test negative

If the result of either the HBV or HCV test was positive, the practice was advised to fax a copy of the result to a secure facsimile number belonging to the research team at Bradford Royal Infirmary, Duckworth Lane, Bradford, BD9 6RJ. The practice was then instructed to invite the participant to the surgery to inform them of this result and to notify them that the research team would arrange an appointment for assessment at Bradford Royal Infirmary.

2.5.6 The HepFree site file

The final stage of the SIV involved reviewing the site file and trial protocol. All members of staff within the practice that were going to be involved with the trial were asked to complete a research specific curriculum vitae (CV) that detailed any previous research experience, a copy of the research CV is available in Appendix 11. They were also asked to sign two registers, one to indicate attendance at the meeting and a second to state that they had received the appropriate training from the trial team to enable them to run the trial. The lead clinician signed the PI agreement page and thereby declared that all research carried out in the practice would be performed in accordance with the research government framework for Health and Social Care (2005) and the World Medical Association Declaration of Helsinki. The PI agreement page is in the trial protocol in Appendix 1.

2.5.7 Participant Retrieval

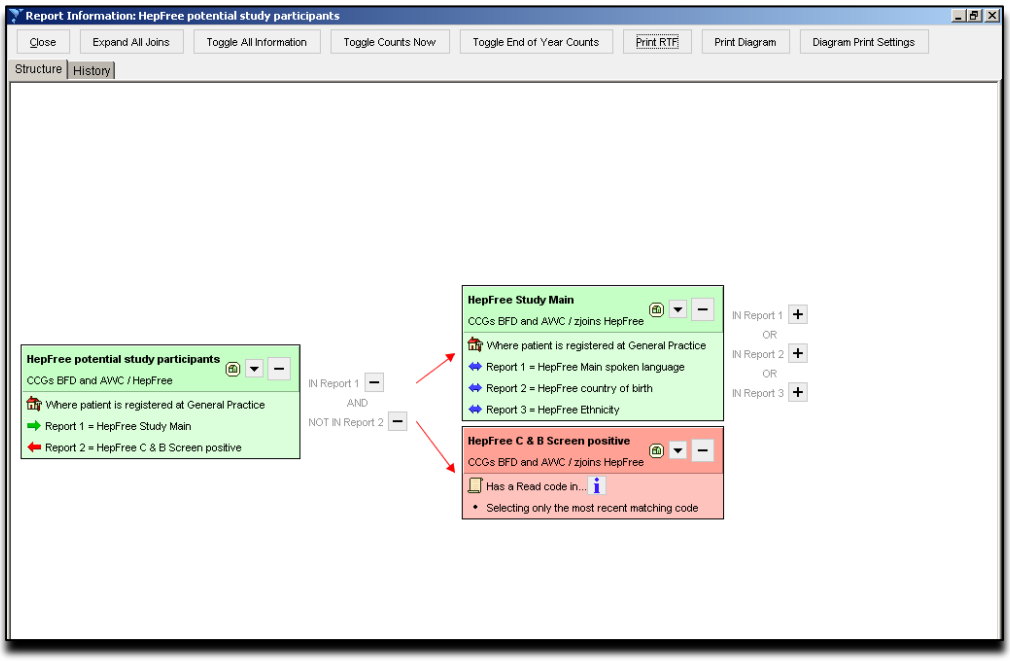
2.5.7.1 Comprehensive enrolment

As discussed above, in order to identify potential trial participants using S1, a series of reports were designed by myself in Bradford, and built with the assistance of the data quality team at the Yorkshire and Humber Commissioning Support Unit, formerly The West and South Yorkshire and Bassetlaw Commissioning Support Unit, West Yorkshire Office, Douglas Mill, Bowling Old Lane, Bradford, West Yorkshire, BD5 7JR. The eligibility search consisted of two reports that were combined and when run at the same time on S1would create the final list of trial participants. Report one searched for Read codes in electronic medical records that related to the following demographic data fields:

- Country of birth
- Main spoken language
- Ethnicity

The second report, report two, was designed to exclude individuals that were eligible based on demographic data searched for in report one, but who had either already been diagnosed with chronic viral hepatitis or had undergone testing for viral hepatitis in the previous five years. The two reports, when run together on the clinical computer system in the GPs produced a final report containing the details of all individuals, registered at that practice that fulfilled the criteria for enrolment. This list was then used by administrative staff within the practice when letters were generated and distributed. Practices recruited to perform comprehensive enrolment were instructed to send an invitation letter to all potential study participants that appeared within the eligibility report during the eighteen month screening period.

Figure 6: HepFree eligibility reports on SystmOne

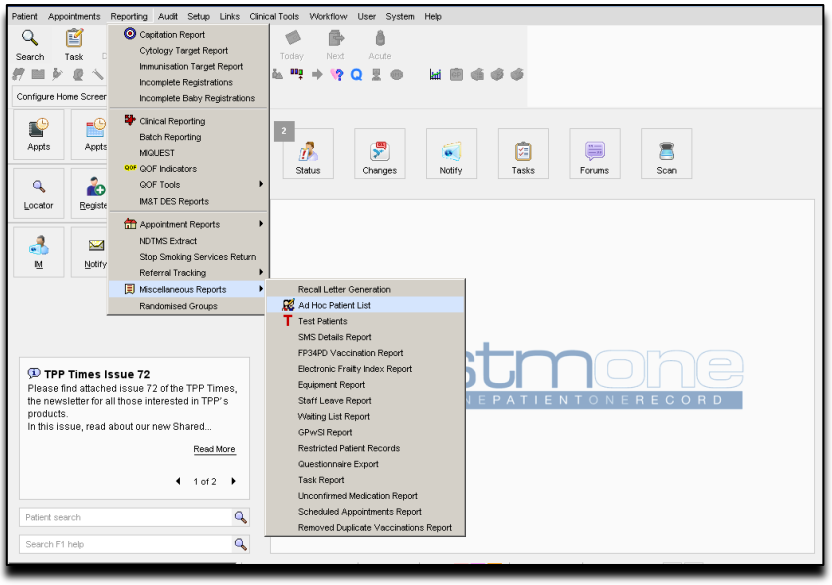


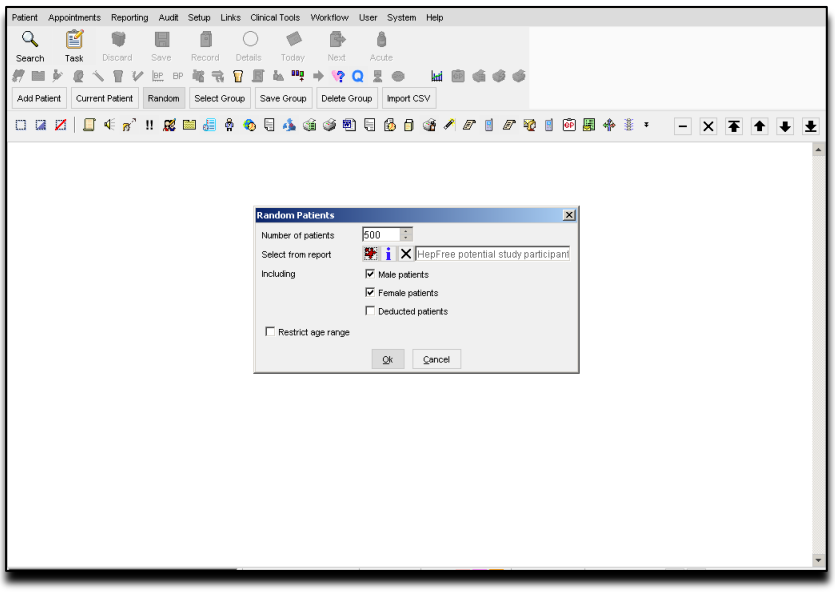
A screen-shot providing an overview of the reports created and published on S1 to identify potential study participants. Report one (HepFree study main) searched for Read codes in individual patient electronic medical records relating to country of birth, main spoken language and ethnicity of interest to the study. Report two (HepFree C & B Screen positive) excluded individuals that would have been eligible for the trial based on demographic data stored within their electronic patient record, but who had either already been diagnosed with chronic viral hepatitis or had undergone testing for viral hepatitis in the previous five years. The two reports, when combined in S1 (HepFree potential study participants) produced a final report containing the details of all individuals, registered at that practice that fulfilled the criteria for enrolment.

2.5.7.2 Selective enrolment

For practices recruited to perform selective enrolment, the same process described above, was used to identify potential study participants registered at the practice. Once the list of study participants had been generated, a function within S1 was used to produce a list of five hundred individuals that were selected at random from the original eligibility report. An additional Read code was entered into the electronic medical record of all five hundred participants, and a new search was created in S1 to produce a report using this Read code. The report produced was a modified list of potential study participants from which the practice could send invitation letters. The Read code selected for use was 9PZ.

Figures 7 and 8: Creating a random list in SystmOne





Screen-shots demonstrating the function available within S1 to create a modified list of potential study participants for use in GP surgeries limited to inviting only 500 of their eligible patient population to participate in the trial following the protocol amendment described in chapter 2.2.3 trial modifications. Potential study participants were selected at random from the original HepFree eligibility report by using the Ad hoc patient list function in S1.

The searches used to identify potential study participants were unique to Bradford because of the different clinical computer systems used in Bradford and London. SystmOne, developed by the Yorkshire based Software Company; The Phoenix Partnership (TPP), Mill House, Troy Road, Leeds, LS18 5TN is the primary care clinical computer system used in all practices in the two Bradford CCGs. In London however, only a minority of practices usedS1, with the majority using EMIS web. EMIS web and S1 utilise different versions of Read codes; Read version 2, and CTV-3 and therefore the searches and reports had to be unique to each particular clinical computer system.

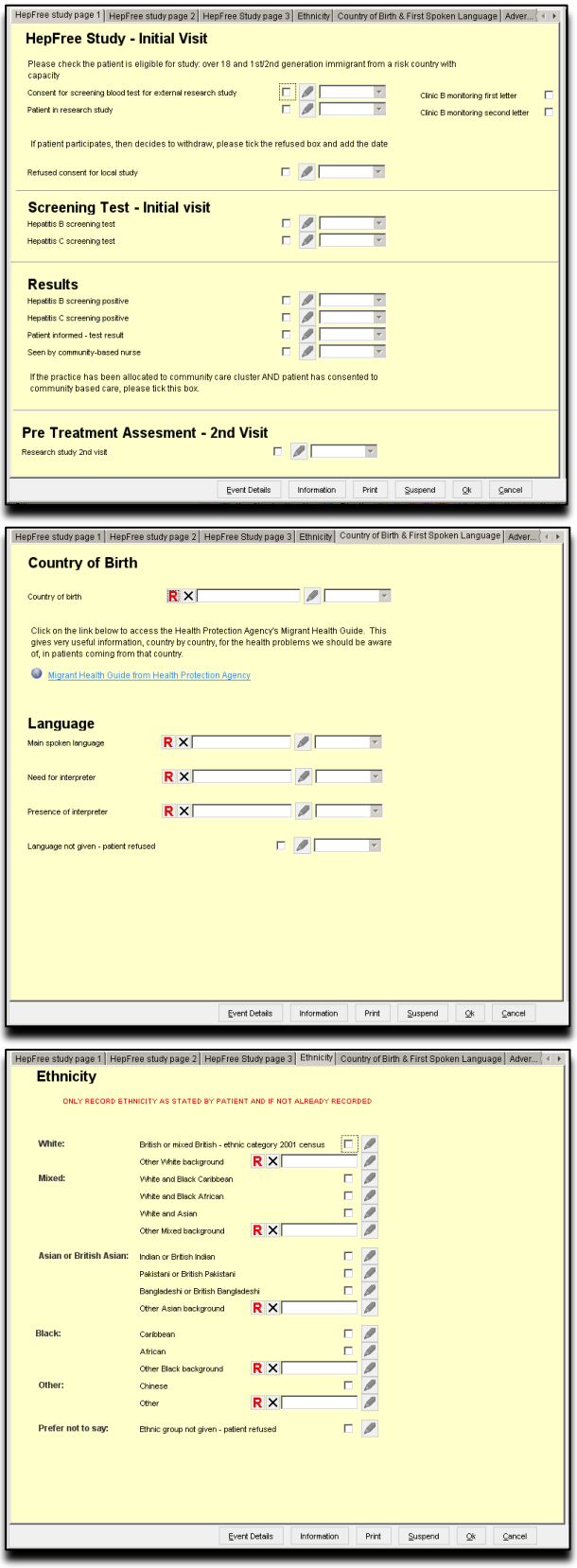
2.5.8 The trial template.

A trial-specific template was designed by the London team with input by me and was built and published on S1 for use by all practices performing targeted testing. The template was used to collect and record specific trial-related activities using Read codes. The following data was recorded in the template either by using a tick box or free text entry. Read codes were attached to all data fields with a tick box.

- The date the individual either agreed or declined the offer to take part in the trial.
- The date consent was obtained from the trial participant.
- The tests requested on the study specific proforma.
- The ethnicity of the trial participant.
- The country of birth of the trial participant.
- The main spoken language of the participant and whether an interpreter was used for the trial consent.

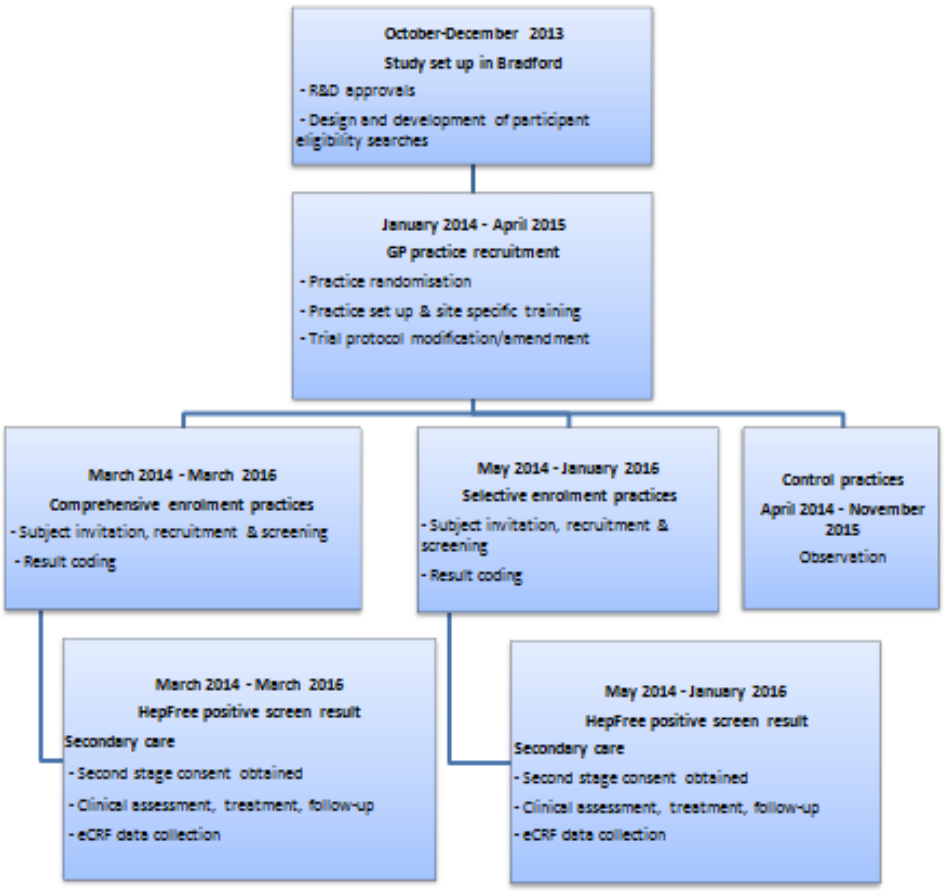
There were two fields on the template to record a positive HBV or HCV test result so either this could be used or the Read codes could be entered manually, as previously described, the second option did not require the template to be opened. In the first week of every month during the testing period, the data quality team initially, but later myself once the contract had expired, produced a series of reports containing cumulative testing data for each practice including all of the data collected in the template, the number of invitation letters sent, the number of individuals that had consented for testing and the results of all viral hepatitis blood tests. The data in these reports was sent to London by secure email for cleansing and storage by the trial data manager.

Figures 9-11: The HepFree trial template



Screen-shots from S1 depicting the trial template and all patient information collected for analysis by the study. The template was completed by healthcare staff within the practice at the visit when consent was sought to perform the viral hepatitis test.

Figure 12: Timeline of HepFree trial related events from October 2013



A flow diagram demonstrating the timeline of trial related events occurring in Bradford from the point that the clinical fellow (myself) joined the HepFree trial. Twenty-one GP surgeries were recruited, randomised and opened between January 2014 and April 2015. Between March 2014 and March 2016, eighteen of the twenty-one practices performed targeted testing for eighteen months and opportunistic testing was performed in the three practices randomised to the control arm of the trial. Participants with a positive hepatitis test during the testing period were invited to attend for a diagnostic assessment, with second stage consent obtained at the first assessment visit that took place in secondary care. All data from the diagnostic and subsequent visits was collected in eCRFs for subsequent analysis.

2.5.9 Trial sample analysis

As discussed in Study Methodology, during the screening visit, six millilitres of venous blood was obtained by venepuncture from each participant and sent with a trial specific proforma for analysis to the virology laboratory at Leeds General Infirmary. Each sample was tested for HBsAg and anti-HCV.

2.5.9.1 Anti-HCV

Samples were tested for the presence of anti-HCV using the Abbott ARCHITECT Anti-HCV assay (Abbott Laboratories. Abbott Park, Illinois, U.S.A.). The ARCHITECT anti-HCV assay is a two-step immunoassay that uses chemoiluminescent microparticle immunoassay (CMIA) technology for the qualitative detection of anti-HCV in human serum and plasma. The test is designed to detect antibodies to structural and non-structural proteins of the HCV genome.

If the result obtained from the ARCHITECT anti-HCV test was positive, the sample was referred for confirmatory testing using the Diasorin Liason XL assay (Via Crescentino snc - 13040 Saluggia (VC)). This test also uses CMIA technology for qualitative detection of anti-HCV. If there was a discrepancy in the results obtained from the first and second tests, a third test was performed on samples using the Orthogenics HCV antibody kit.

HepFree study samples tested for anti-HCV were reported in one of three ways as listed below in addition to subsequent actions that were taken as part of the trial.

2.5.9.1.1 Anti-HCV positive

Samples that tested positive for anti-HCV were automatically referred for RNA testing by the virology laboratory to confirm chronic infection status. This was performed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, Roche Molecular Diagnostics (4300 Hacienda Drive, Pleasanton, CA 94588, USA). This is an in-vitro nucleic acid amplification test for the quantification of HCV in human plasma or serum.

2.5.9.1.2 Anti-HCV negative.

The blood test for HCV was negative and no further action was needed.

2.5.9.1.3 Low level anti-HCV

For samples that were reported as low level antibody or antibody indeterminate by the virology laboratory, the study participant was recalled for repeat anti-HCV testing after seven days. If the repeat sample was positive for anti-HCV, RNA testing was performed, and if it was either negative, or indeterminate again, no further action was taken.

2.5.9.2 HBsAg

Blood samples were tested for HBsAg using the Abbott ARCHITECT HBsAg qualitative assay, a one-step immunoassay for the qualitative detection of HBsAg using CMIA technology. All samples that tested positive for HBsAg using the Abbott immunoassay underwent confirmatory testing using the Diasorin Liason XL assay in addition to testing for the following markers to confirm chronic infection: total core, core IgM, Hepatitis B e-antigen and hepatitis B e-antibody.

2.5.10 HepFree: second stage

As discussed, all participants with a positive hepatitis result were contacted by a member of staff in the practice and an appointment made to discuss the significance of the positive result with one of the clinicians within the practice. The trial clinical fellow was informed of the positive result by the practice and was responsible for generating a referral for the participant to attend secondary care for a diagnostic assessment (myself in Bradford). The participant was notified of this appointment by a letter to their home address and text message reminder.

Irrespective of the randomisation outcome regarding location of treatment services, all participants had their initial diagnostic assessment performed in secondary care. All appointments that occurred following a positive screening test were conducted by me.

On the day of the appointment, once the study participant had arrived in the outpatient department at Bradford Royal infirmary, they were introduced to one of the hepatology research nurses. The role of the research nurse was to counsel the participant on the second-stage of the trial and seek consent from them to remain in the trial; a copy of the second stage consent form is available in Appendix 12. The participant was informed that if they chose to continue in the trial they would be randomised to receive treatment for viral hepatitis if required, and would be invited to attend all subsequent follow up appointments either in hospital (standard care) or in the community. Prior to giving consent, participants were provided with an information leaflet pertaining to stage-two, included in Appendix 13. As HepFree was a cluster trial, GPs were randomised to either standard care or community care follow-up and all participants registered within the practice would be randomised to the same treatment location. The process outlined above, whereby a research nurse, associated with the trial, but who was unaware of the practice allocation obtained consent from the participant to participate in the second-stage of the trial ensured that inadvertent bias was avoided and individuals were truly blind to their treatment allocation when they consented to participate.

For participants randomised to community care follow-up, after the initial diagnostic assessment and any appointments required for radiological examinations that formed part of the diagnostic assessment, all follow-up appointments were conducted in the community. The one exception to this was when individuals were assessed by a viral hepatitis clinical nurse specialist (CNS) with a view to commencing antiviral therapy. These assessment appointments were performed in the secondary care to ensure that the CNS did not identify any issues that would prevent an individual from being able to be treated safely with antiviral therapies outside of the hospital setting.

2.5.11 Community treatment in HepFree

One of the objectives of the HepFree trial was to examine the impact of moving the location for treatment and follow-up of viral hepatitis from secondary care to the community,

measured in terms of patient adherence and compliance. In Bradford I approached two GPs and requested to use a consulting room in each in order to set up a satellite hepatology clinic. Practices were reimbursed financially from the trial for the number of hours the room was used by a member of the research team.

Practices were selected primarily according to their location. I selected practices that in theory would be easier for participants to access taking into account the distance they would have had to travel to the hospital compared to the community clinic. It was not feasible to calculate the distance for each individual from their home address to the hospital so we calculated distance from their base GP surgery and selected locations that were both closer than Bradford Royal Infirmary in distance, and that had facilities for the study participants to use free of charge, such as parking.

2.6 Exploratory analysis of findings from practices performing comprehensive enrolment.

Data obtained from ten practices assigned to perform comprehensive enrolment that had completed eighteen months of testing by March 2016 were used in an exploratory analysis performed by myself, and presented in this thesis. I used the data available to investigate the feasibility and acceptability of targeted testing for viral hepatitis in immigrant populations in primary care. Of particular interest to me were the demographics of individuals who consented to testing, and those who declined the offer, drawing comparisons with the populations that were eligible and invited to participate in the trial. Other objectives I wanted to investigate included whether the type of letter invitation used had an impact on response rates. In addition to this, I explored the timing of response between the date the invitation letter was sent and when the screening test was performed. Through analysis of this data I wanted to gain more information and attempt to draw conclusions on the effectiveness of letter invitation in preventative testing strategies in immigrant populations.

The exploratory analysis used a combination of descriptive and inferential statistical tests performed using IBM SPSS statistics 23 and Microsoft EXCEL. Independent T-tests, Chi-square tests of independence, Fisher's exact tests and logistic regression were performed in SPSS.

2.7 The HepFree sub-study

In this section I will discuss the methodology of the HepFree sub-study, designed and conducted to investigate symptom prevalence and use of healthcare resources in primary care by individuals with a positive HCV screening test.

The HepFree sub-study was a retrospective, observational case-control study investigating symptoms and primary care healthcare resource utilisation in individuals with a positive HCV test. It was conducted in participants that had been enrolled into, and consented to testing for viral hepatitis in the main HepFree trial in Bradford. The sub-study was designed to test the following hypotheses:

- Individuals with undiagnosed chronic HCV (RNA positive) use healthcare resources in primary care more frequently compared to individuals that have no evidence of infection with viral hepatitis (hepatitis B and C).
- Individuals with evidence of past infection with HCV, but no evidence of on-going infection (anti-HCV positive, RNA negative) do not have an increased number of episodes of attendance to primary care compared to individuals with no evidence of previous infection with viral hepatitis.

2.7.1 Sub-study set up

This retrospective, observational case-control study was designed, developed and run solely by the clinical trial fellow (myself) in Bradford. Funding for the sub-study was provided by the main HepFree trial. The HepFree trial CI supervised and oversaw all sub-study activities.I designed and wrote the protocol for the sub-study and completed and submitted the IRAS form. Sub-study documents were submitted for review by the Bart's Health NHS Trust Research Development team, Joint Research Management Office (JRMO), Queen Mary Innovation Centre, Lower Ground Floor, 5 Walden Street, London, E1 2EF and subsequently underwent internal peer review at the Blizard Institute, 4 Newark Street, London, City of London, E1 2AT. Provisional sponsorship was sought from the Joint Research Management Office for Bart's Health NHS Trust and Queen Mary University London, Mile End Road, London, E1 4NS. Once sponsorship had been agreed, sub-study documents were submitted for central ethics review to the London-West London & GTAC Research Ethics Committee, The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS. Following a committee meeting at

the Hammersmith Hospital, London, W12 0NN, central ethics approval was granted and Queen Mary University London subsequently provided full sponsorship. Once all agreements were in place, data collection began in all practices performing targeted screening in Bradford.

2.7.2 Sub-study Methodology

2.7.2.1 Participant selection: cases

All cases and controls included in the sub-study had been recruited, consented and undergone testing for viral hepatitis as part of the main HepFree trial between March 2014 and February 2016. In order to test the hypotheses described above, data for analysis on healthcare utilisation was collected on two cohorts of cases; 31 cases of chronic HCV infection (characterised by anti-HCV positive, RNA positive) and 23 cases with evidence of previous HCV infection associated with spontaneous clearance (characterised by anti-HCV positive, RNA negative without prior antiviral therapy or medical intervention). Cases were diagnosed using the ABBOTT ARCHITECT Anti HCV chemiluminescent microparticle immunoassay (Abbott Laboratories. Abbott Park, Illinois, U.S.A) and RNA positive using the Roche COBAS Ampliprep/COBAS Taqman HCV test (Roche molecular diagnostics, 4300 Hacienda Drive, Pleasanton, CA 94588, USA). A detailed description of the definitions of cases is listed below.

As discussed previously, in the main HepFree trial, all participants with a positive HCV test were invited by the research team for assessment in secondary care. At this appointment, for individuals with evidence of previous infection with HCV, a thorough medical history was taken to ensure they had not received eradication therapy; this was an exclusion criterion for the sub-study. Separate consent was not obtained from participants for the sub-study as permission was sought during the initial consent process.

2.7.2.2 HepFree sub-study definitions

Cases of chronic HCV infection were diagnosed by the presence of both anti-HCV and HCV RNA. Cases with evidence of previous infection associated with spontaneous clearance were diagnosed by a positive anti-HCV test, but a negative RNA test.

2.7.2.3 Sub-study criteria for enrolment

Individuals that were identified as cases and included in the sub-study fulfilled the following criteria:

- Registered at a HepFree targeted screening GP surgery.
- Enrolled, consented and tested for viral hepatitis as part of the HepFree trial between March 2014 and February 2016.
- Had a blood test result consistent with either chronic HCV or evidence of previous infection with HCV.

Exclusion criteria for the sub-study were as follows:

- Anti-HCV positive cases in whom the individual had previously received antiviral therapy for the treatment of HCV.
- Individuals with an indeterminate anti- HCV antibody test result.
- Individuals that did not engage with follow-up in the HepFree trial (also known as lost to follow up).
- Individuals that died during follow-up in the HepFree trial
- Individuals that withdrew consent to continue in the HepFree trial.

2.7.2.4 Participant selection: controls

For the purpose of the sub-study, a control participant was defined as an individual that had been recruited, consented and had undergone testing for viral hepatitis as part of the HepFree trial. The control must have tested negative for both HBV and HCV. Controls were matched to cases using the following criteria:

- Gender
- Age; documented date of birth within six months
- Country of birth
- Ethnicity
- Length of time living permanently in the UK: documented date of entry of the control within six months of the case.

Participants selected to act as controls were identified and matched to cases by creating and running a report in S1. All eighteen GP practices that were performing targeted testing in the HepFree trial were used to search for participants to act as controls.

In HepFree, each participant that was consented and had a viral hepatitis blood test as part of the trial had a trial specific proforma completed by a member of staff within the practice (described in section 2.5.8). As previously discussed, this proforma contained demographic details for each participant in addition to information relating to the date and time that they underwent testing. Data entered into the proforma was recorded as Read codes in each patient electronic medical record. A report could therefore be created and run on S1 to identify all individuals registered in each HepFree practice that had a Read code within their electronic records stating that they had undergone testing through HepFree.

The list of participants generated by the report was then broken down by gender and age to create a final list of participants. Once eligible controls had been identified based on age and gender, as described above, the clinical fellow reviewed the demographic data stored on within the patient electronic medical record on S1 to validate eligibility based on the remaining matching criteria (country of origin, length of time resident in the UK) and confirmed that the viral hepatitis diagnostic test results were negative. A control was excluded if the clinical fellow was not able to fully match them to a case using information stored in the electronic medical record. This process of selecting a control subject for a case

was repeated on each clinical computer system in all of the practices performing targeted screening.

In cases when more than one eligible control participant was identified using the criteria for matching stated above, a randomisation programme on Microsoft EXCEL was used to select the final participant that would act as the control. In S1, demographic data is stored in a separate area to the journal, where details of consultations are documented so the clinical fellow was blinded to any clinical information until after the control participant had been selected and prevented selection bias from being introduced. Cases were matched to controls using a 1:1 ratio.

In the event that a suitable participant to act as a control could not be identified using the above criteria, the six month matching rules for date of birth and/or length of time in the UK were extended, with controls selected that fulfilled the matching criteria as close as possible.

2.7.3 Sub-study data collection

In order to test the hypotheses, data was collected on the total number of episodes of care sought by cases and compared to controls, up to, and including the visit when the individual was enrolled into the HepFree trial. An episode of care was defined as any documented contact with a healthcare professional within the GP practice. A healthcare professional for the purpose of this sub-study was defined as a doctor, specialist nurse practitioner, practice nurse, community nurse, district nurse or healthcare assistant. For each episode of care that was documented within the electronic patient record, the following information, where available was collected: the date of attendance and the diagnosis or outcome of the episode of care.

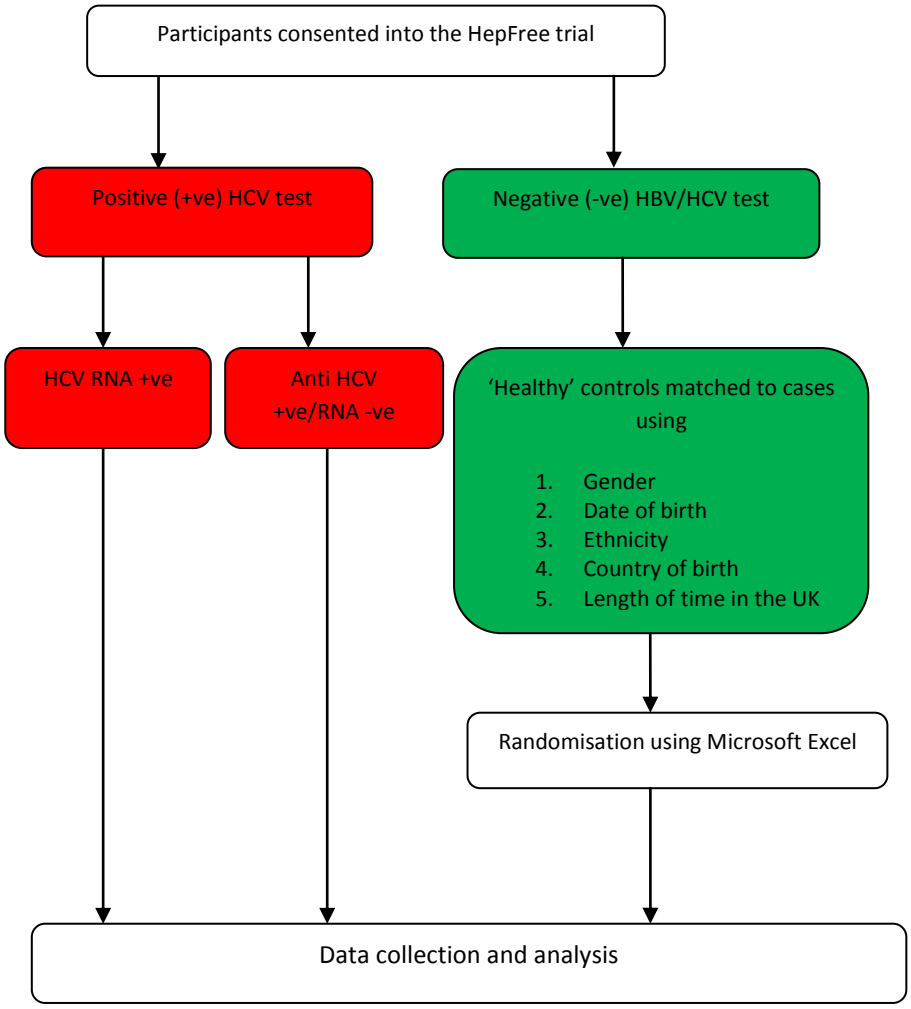
For participants that had lived in the UK prior to 2005, data was collected from 01/01/2005. This cut-off date was selected as from this point; attendances to primary care were recorded and available to view in the electronic medical record on S1. For participants that entered the UK after 2005, data collection commenced from the time of the new-patient registration appointment.

Sub-study data was anonymised using the strategic identifier (ID); a pseudoanonmyised number generated by the clinical computer system in primary care at the point of enrolment into the HepFree trial. All data collected for analysis was stored using this number in a Microsoft EXCEL database on a secure hospital information technology (IT) server. Supplementary demographic data collected by the HepFree trial was accessed for the sub-study. The flow diagram in Figure 13 summarises participant selection for the HepFree sub-study.

2.7.4 Statistical analysis

Descriptive analysis was carried out in Microsoft EXCEL. Statistical analysis was performed by an independent statistician. Poisson and negative binomial based generalised linear models were fitted in STATA 14 using Generalised Estimating Equations with an autoregressive correlation matrix of order 1 (AR1). Relative risks were estimated using the univariate negative binomial model.

Figure 13: Participant selection for the HepFree sub-study



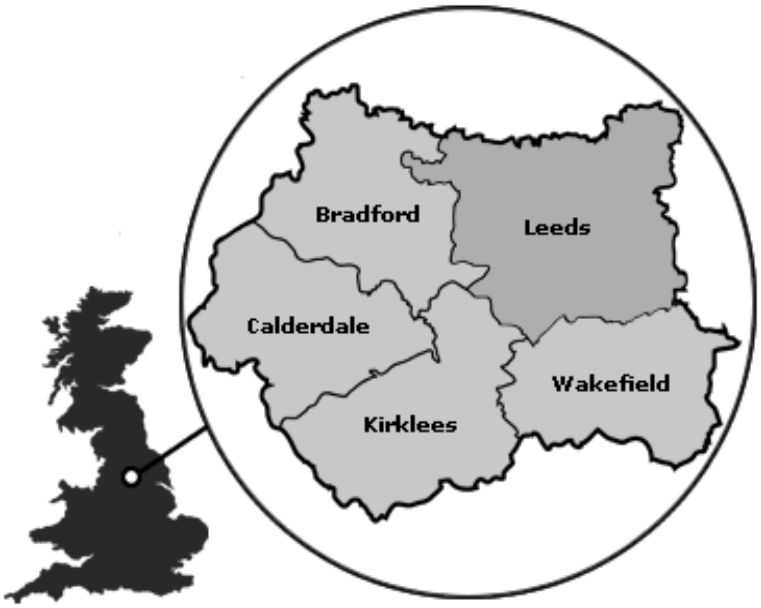
A flow chart summarising participant selection in the HepFree sub-study. Individuals with a positive test for HCV diagnosed through the HepFree trial were identified and screened against the inclusion criteria for the sub-study. If eligible, they were divided into two groups; RNA positive chronic HCV and anti-HCV positive, RNA negative (previous infection with spontaneous clearance of HCV). Individuals recruited to HepFree with a negative test for HBV and HCV (healthy controls) were matched to cases in a 1:1 ratio using the criteria detailed in the green box. If more than one healthy control was identified as a match, a programme in Microsoft Excel was used to select a participant at random to act as the healthy control. Once controls had been matched to all cases, the electronic medical records of each participant were accessed to collect data for analysis.

3. Results: Demography of the area.

3.1 Overview

In this Chapter I will review both the demography of Bradford and the practices participating in HepFree. In Bradford, twenty-one GP practices were recruited and randomised to rake part in the HepFree trial.

Figure 14: The city of Bradford and surrounding areas



A map of Great Britain with a pin denoting the location of Bradford and its surrounding areas.

3.2 Bradford: census summary.

Information accessed from UK census data.

Bradford is a city and metropolitan borough located in West Yorkshire, England. According to the Office for National Statistics, it has a population of 528, 200, making it the fourth most populous metropolitan district, and sixth most populous local authority district in England.

The city of Bradford is situated on the edge of the Pennines, bound to the east by the city of Leeds, to the west by the Pendle borough of Lancashire, to the north by the boroughs of Craven and Harrogate, and to the south by the metropolitan boroughs of Kirklees and Calderdale.

Bradford rose to prominence as an international centre of textile manufacture, in particular wool, during the 19th century. This later fell into decline in the mid-twentieth century. Similarly to other post-industrial areas in the north of England, Bradford has faced the challenges of deindustrialisation, social unrest and economic deprivation as a result of this decline in industry.

Bradford has a long history of immigration, making it one of the north of England's most culturally and ethnically diverse cities. Data from the 2011 census suggested that 20.4% of Bradford's population were of Pakistani origin. There has been a rise in the settlement of people of Pakistani origin since the last census in 2001, in which only 14.5% of the city's inhabitants belonged to this ethnic group. In the 2011 census, 76.6% of Bradford's population held a UK passport, 3.9% held a passport from either an Asian country or country in the Middle East, 2.8% held one from a country within the European Union, and 16.3% of the population held no passport.

More recently, a rapid increase in the number of migrants residing in Bradford has been observed. Between 2001 and 2011, 40, 975 (45.7%) of non-UK born residents arrived in the city to live, and of these, 32,290 arrived after 2004.

In 83.1% of households included in the 2011 census, all residents aged sixteen or over had English listed as their main spoken language. In 8.4% of households, at least one adult could speak English, in 1.5% of cases, no adults could speak English but one or more children could speak English, and in 7.1% of households, none of the residents were able to speak English.

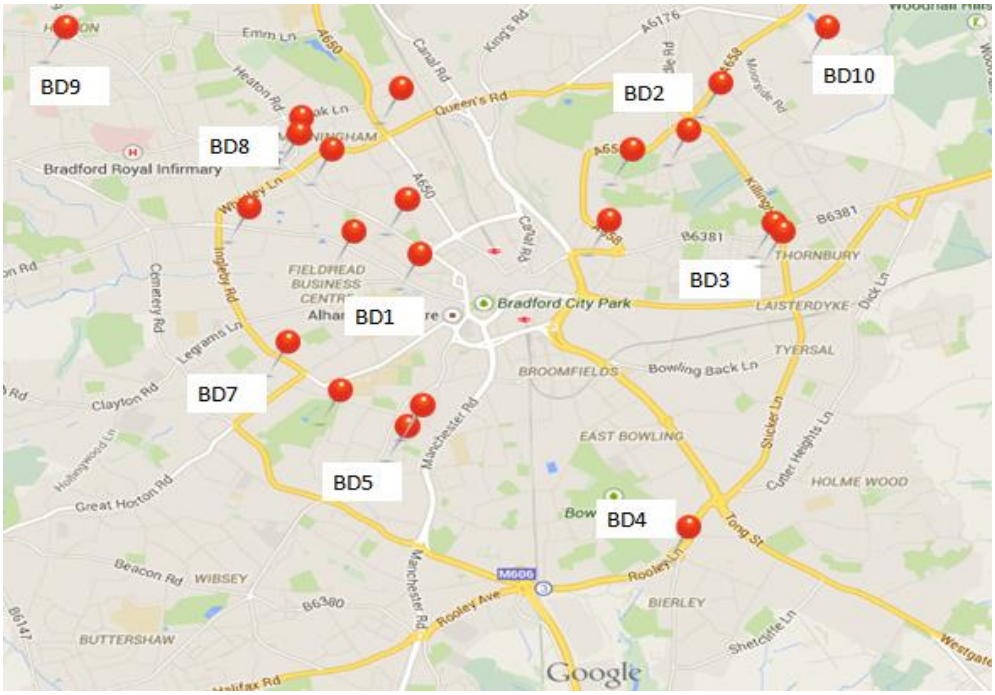
Almost 25% of Bradford's population listed their primary religion as Muslim. A reduction in the number of residents with Christianity as their chosen religion has been observed, from 60.1% in 2001 to 45.9% in 2011. In 20.7% of cases participants had no religious preference and in 6.2% of cases the question was not answered.

Areas of Bradford are among the worst in the UK in terms of the level of social deprivation. According to the census occupancy rating, nearly 10% of households were classed as overcrowded. Within West Yorkshire, Bradford has the fewest number of economically active residents aged between sixteen and seventy-four. At the time of the last census there were 210,000 residents aged between sixteen and seventy-four in employment, corresponding to an employment rate of 57.3%, compared to a regional rate of 60.0% and a rate in England of 62.1%. The largest industry in Bradford was noted to be retail/wholesale, with 17.7% of Bradford's employed residents working within this field.

3.3 GP practices in Bradford

There are two CCGs in Bradford; Bradford City comprising twenty-seven GP practices that serve the local population, and Bradford District consisting of forty practices. Permission was granted to recruit practices from within both CCGs to conduct the HepFree trial. GP practices in the postcode districts BD7, 8 and 9 were prioritised in terms of recruitment as census data demonstrated that large groups of ethnically diverse individuals resided within these areas; individuals that would fit the inclusion criteria of HepFree. Figure 15 demonstrates the locations of GP practices recruited to participate in the HepFree trial.

Figure 15: Locations of HepFree in Bradford



A map of GP surgeries that were recruited to the HepFree trial in Bradford. Red pins demonstrate the location of practices within each postcode district. GP surgeries in BD8 were prioritised during practice recruitment as these areas have high numbers of ethnically diverse populations residing within them.

In August 2013, prior to the trial permissions being granted, a meeting with clinicians from GP practices within both CCGs was held by the research team to raise awareness and assess interest in the trial. Contact details were taken for clinicians interested in participating at the time of the meeting. When recruitment commenced in January 2014, these practices were approached in the first wave of recruitment.

As previously discussed in Materials and Methods, each practice was contacted via telephone to assess interest and offer them a place in the trial, followed by an email summarising the key points of the discussion as well as details of a member of the research team to contact in the event of further questions. This email was sent immediately after the telephone call. In Bradford, I as the clinical fellow was solely responsible for recruiting the twenty-one practices included in the trial.

In the majority of cases, due to the work pressures, it was not possible to speak directly to the clinician with regards to participating in the trial. Often the practice manager acted as the spokesperson for the practice. In most cases, the practice manager agreed to discuss the trial on our behalf, at the practice meeting, where the clinicians would be present. This meeting would occur either once per week or once per fortnight. If the time between the initial telephone call and the practice meeting was more than seven days, I would endeavour to speak to the practice manager again to ensure that the trial was added to the meeting's agenda.

Response to trial recruitment efforts was variable; from the list of clinicians that expressed an initial interest in the trial in August 2013, 82% of practices agreed to become trial sites. GP practice recruitment commenced in January 2014 and was completed in April 2015.

3.4 Summary of recruitment

In five out of the twenty-one practices (24%) that were recruited and opened, the research team was approached by the practice managers of the sites. In these cases, the practices had positive feedback from other trial sites that were already open and recruiting participants into HepFree. In two cases (9.5%), the practices had previously been approached regarding recruitment by the clinical fellow, but had declined. However, during the period of

recruitment between January 2014 and April 2015, the practice managers in charge of the practices changed, enabling the sites to be subsequently recruited by the clinical fellow. As discussed in Materials and Methods, at the time of the telephone call the research team offered to attend the practice to discuss the trial in more detail. Alternatively, if this was not required and the site agreed to participate, details required for randomisation were collected by the practice staff using the HepFree eligibility searches that had been published on S1 and were available to access by the practice staff. The eligibility searches, as described in Materials and Methods, were the series of reports created by the research team that enabled potential study participants in each practice to be identified.

Once the outcome of randomisation was known, the practice was contacted to arrange a mutually agreeable time for the SIV. Table 6 summarises the time between first contact with practices and site initiation, including the number of episodes of contact that were initiated by the clinical fellow within the research team.

Table 6: GP surgeries recruited to the HepFree trial

Recruitment details for practices that agreed to participate in HepFree including the number of episodes of contact between the practice and the research team and the number of days that elapsed between the first episode of contact and the site initiation visit. The average number of episodes of contact between the research team and practice was 8, range 2 – 22.

Practice	Date of first contact	Date of sign up	Date site opened	Number of episodes of contact	No. of days elapsed from first contact to site initiation
1	13/11/2013	13/11/2013	14/04/2014	3	152
2	13/01/2014	24/01/2014	07/04/2014	6	83
3	14/01/2014	20/01/2014	08/04/2014	7	84
4	14/01/2014	13/02/2014	02/04/2014	5	78
5	14/01/2014	04/02/2014	10/03/2014	4	55
6	15/01/2014	10/02/2014	07/05/2014	14	112
7	16/01/2014	11/02/2014	07/05/2014	17	111
8	04/02/2014	01/05/2014	02/05/2014	8	87
9	04/03/2014	27/03/2014	05/08/2014	22	155
10	21/03/2014	28/03/2014	30/04/2014	4	40
11	21/03/2014	01/04/2014	22/05/2014	5	65
12	31/03/2014	01/04/2014	01/05/2014	4	30
13	01/04/2014	03/04/2014	01/05/2014	3	31
14	03/04/2014	14/04/2014	02/05/2015	7	397
15	03/04/2014	04/07/2014	09/06/2015	13	432
16	09/04/2014	09/04/2014	30/04/2014	2	21
17	08/07/2014	24/07/2014	09/10/2014	8	93
18	19/09/2014	19/09/2014	16/10/2014	3	27
19	12/01/2015	28/01/2015	17/04/2015	9	95
20	13/02/2015	08/03/2015	10/04/2015	7	56
21	13/02/2015	08/03/2015	10/04/2015	7	56
AVERAGE				8	108

On average, eight episodes of contact by the clinical fellow were required to recruit a practice and 108 days elapsed between first contact and site initiation. Practice 1 was the first site recruited and this was used to evaluate both recruitment and trial procedures. Specifically, the trial statisticians, once formal ethics and Research and Development office approvals were in place, tested the randomisation programme using data from this practice to ensure it was functioning prior to full recruitment commencing. Up until the approvals were in place, all testing of the randomisation programme had been conducted on dummy data. Due to the practice being used to test trial related processes, there was a prolonged delay between first contact and site initiation. In addition to practice 1, practices 2, 3, 4 and 5 were contacted by the fellow and all agreed to participate in the trial prior to R&D permissions being granted; however none of the practices were opened until all required permissions were in place. Hence some of the delay from site contact to initiation that was observed was due to trial related logistical concerns.

The reason for delayed site initiation in the cases of practices 6 and 7 were staff sickness within the practices. When practice 8 was approached by the trial team, the offer to participate was initially declined because of long-term vacancies in staff posts; however the practice manager later contacted the trial to make enquiries regarding HepFree and was subsequently recruited.

The time between first contact and site initiation exceeded 150 days in practice 9. The reasons for this delay were initially because the practice moved locations to a new site and building within Bradford. Secondly, this practice was one of the few recruited that would ordinarily not send blood samples to Bradford Royal Infirmary for analysis, but to another hospital laboratory within the region. As the trial had an agreement in place with Leeds Teaching Hospitals for analysis and reporting of trial samples, a bespoke agreement had to be created with the practice to ensure the safe and confidential transfer of all study bloods to Bradford as opposed to the other laboratory. The pathology laboratory at Bradford Royal Infirmary then organised the safe and secure transfer of all samples to Leeds for testing.

Practices 14 and 15 were opened more than twelve months after the point of first contact by the study team. This was because these practices were recruited to also participate in a sub-study associated with the main trial that assessed individuals pre-existing knowledge of and

attitudes towards viral hepatitis. For the sub-study, all eligible participants registered in the practices were contacted prior to receiving the invitation for testing and given the opportunity to participate in this additional study. If an individual decided to participate in the sub-study, a questionnaire was completed with them over the telephone. Practice 17 was initially also approached to conduct the sub-study, however it was later not required, and so subsequently opened to recruit for the main trial only. Practices 16, 18, 19, 20 and 21 approached the trial clinical fellow and requested to take part and be randomised.

In the initial cluster design, Bradford was designated 18 sites to recruit and open, however due to difficulties with recruiting sites to perform HepFree in London, additional trial sites were allocated to Bradford and this allowed the research team the opportunity to offer places for practices 19, 20 and 21. For reasons stated above, there was no typical trial contact and initiation procedure and it is difficult to draw general conclusions from these data about the logistical difficulties that would be involved in any general role out of GP based screening. However the myriad of contractual and logistical issues, not all of which were trial related, indicate that any large scale screening programme would require considerable logistical support. Table 7 summarises the outcomes for practices that were contacted by the trial fellow but declined to participate in HepFree.

Table 7: GP surgeries that declined HepFree participation

Details of practices that declined the invitation to participate in the HepFree trial including the number of episodes of contact between the trial team and the GP approached and reasons provided by the practice for declining.

Practice	Date of first contact	Date practice declined to participate	No. of episodes of contact	Comments
22	15/01/2014	15/01/2014	1	Single attempt to speak to practice manager, advised to contact by email. Trial synopsis and contact details sent. Email declining the offer to participate received from the practice manager on the same day that first contact was made.
23	10/02/2014	24/02/2014	3	Trial discussed with practice manager on the phone. Two further emails sent offering a face to face meeting, trial place declined.
24	01/04/2014	13/05/2014	6	Trial discussed with practice manager on telephone who agreed to discuss at the practice meeting. Four email reminders sent. Study discussed 13/05/2014, trial team contacted by practice manager to explain that the trial place had been declined by the clinicians due to increased perceived work load associated with the trial. Declined offer of a face to face meeting to explore concerns
25	01/04/2014	No formal response from practice	4	Trial discussed with practice manager on the phone. Three follow up emails sent with no response.
26	07/04/2014	07/04/2014	1	Single attempt to speak to practice manager, advised to contact by email. Trial synopsis and contact details sent with email response from the practice manager received on the same day.
27	07/04/2014	08/04/2014	2	Trial discussed with practice manager on telephone who agreed to discuss at the practice meeting on the following day. Contacted by practice manager to explain that the trial place had been declined by the clinicians, no reason for refusal stated in email. Declined offer of a face to face meeting to explore potential concerns.

Table 7: GP surgeries that declined HepFree participation

Details of practices that declined the invitation to participate in the HepFree trial including the number of episodes of contact between the trial team and the GP approached and reasons provided by the practice for declining.

Practice	Date of first contact	Date practice declined to participate	Number of episodes of contact	Comments
28	08/04/2014	25/04/2014	4	Telephone call and email sent to practice manager. Two further email reminders sent regarding the study. Declined to participate due to pre-existing work pressures within the practice.
29	14/04/2014	13/06/2014	7	Trial discussed with lead GP on telephone who expressed an interest in participating. Subsequent difficulty engaging the practice to enable trial randomisation. Five follow up emails sent and one further telephone call with lead clinician of practice who declined due to perceived increased work load associated with the trial. Declined offer of a face to face meeting to explore concerns.
30	14/04/2014	01/05/2014	7	Three attempts to speak to practice manager by telephone, unsuccessful. Contacted CCG lead who discussed with the practice on behalf of the trial. Face to face meeting with lead GP and practice manager. Declined offer of trial place with 'cap' of only inviting 500 participants.
31	14/01/2014	14/01/2014	1	Trial discussed with practice manager, declined due to problems with long-term vacancies. Declined offer of a face to face meeting.
32	21/04/2014	21/04/2014	2	Trial discussed with practice manager, declined due to perceived increased work load associated with study. Declined offer of a face to face meeting to further explore concerns

From R&D approvals, it took fourteen months to engage and recruit twenty-one practices to the trial. From all practices approached, 38.9% participated in the trial.

Once practices had been recruited, randomised and opened, the locations for the community clinics were decided. As discussed in Materials and Methods, one of the objectives of the HepFree trial was to examine, by measuring patient adherence and compliance to both appointments and therapies, the impact of moving the location for treatment and follow-up of viral hepatitis from secondary care to the community. In Bradford I approached two practices that had been recruited to the trial and requested to use a consulting room in each one in order to set up a satellite hepatology clinic. Practices were chosen primarily on their location, selecting practices that would be closer in distance for participants to access compared to the hospital. As it was not feasible to cater for all participants by calculating the distance from their home address to the hospital, we decided to calculate distance using the address of their base GP to both the community clinic and the hospital, as patients have to live within a certain catchment distance of their surgery. In addition to selecting locations closer in distance compared to the hospital, we ensured there were facilities available for the trial participants to use free of charge, including parking. What we failed to consider when selecting the locations for community clinics were the public transport links that would be available for use by patients randomised to this arm of the trial.

The distances of practices randomised to the community arm of the trial to both of the satellite clinics and the secondary care centre (hospital) are displayed in Table 8.

Table 8: Locations of all HepFree GPs in relation to secondary care and community based hepatology satellite clinics

The distances in miles from each HepFree practice to Bradford Royal Infirmary, Duckworth Lane, Bradford, BD9 6RJ (the location used to perform follow-up of positive participants assigned to standard of care) and the two GPs where satellite hepatology services were set up for use by the HepFree trial. The 'designated community centre' is the satellite clinic where participants would be followed-up in the event that their practice had been randomised to the community follow-up nested intervention.

Practice	Satellite clinic 1 (miles)	Satellite clinic 2 (miles)	Secondary care (hospital) (miles)	Designated community centre
A	2.3	0.8	3.1	2
B	2.5	1.3	3.3	2
C	2.7	2.6	2.7	2
D	0.3	3.0	1.1	1
E	0	2.9	1.0	1
F	1.3	2.1	2.2	1
G	2.1	1.0	3.0	2
H	3.6	2.0	4.4	2
I	1.6	3.0	2.2	1
J	2.9	0	3.7	2

3.5 Discussion

The purpose of HepFree was to determine whether or not it would be feasible to implement a screening programme for viral hepatitis in GP. The data presented here demonstrates that the task of recruiting and persuading practices in primary care to test immigrants is by no means trivial.

A recruitment rate of less than 40% in all practices approached regarding HepFree indicates that staff within practices were somewhat reluctant to adopt the trial and offer testing for viral hepatitis to the high-risk populations registered there. Although in this thesis I will not

comment specifically on recruitment methods and subsequent uptake rates in London, similar difficulties were encountered there and resulted in the trial increasing the number of sites in Bradford.

As mentioned above, it is important to consider the amount of effort required to engage the practices that did eventually become trial sites. It took an average of eight episodes of contact, ranging from a minimum of two to a maximum of twenty-two, and an average time of 108 days elapsed from the first point of contact with a practice to the site been opened for recruitment. Although some extenuating circumstances were identified including delays related to study approvals from R&D, in the majority of cases, the delays encountered were due to routine problems frequently encountered in the work place, including staff sickness, and post vacancies. In Bradford, one of my main roles in HepFree initially was to recruit and set up practices, and therefore I was able to dedicate a large amount of time and effort to this task. This ensured that we had sufficient sites recruited to fulfil the study design.

It became evident early in the process of recruitment that attempting to implement a protocol that could be used to engage and recruit practices would be difficult. This was probably, largely due to the fact that we were asking practices to adopt and conduct the trial on our behalf, and therefore we had to be mindful of both the pre-existing work load within the practice as well as the demands already placed on practice staff. Analysis of recruitment outcomes in Table 6 demonstrated that there was no typical contact and initiation procedure, and bespoke methods were employed in order to recruit practices.

Despite the study providing financial incentives, it was not possible to engage some GP practices with the case-finding project. Taking all of this into account, if the combined results of the HepFree trial recommend universal screening for viral hepatitis in migrant populations in primary care, it would be beneficial to conduct further qualitative research in a selection of practices, ideally including practices that both adopted the trial in addition to some that declined to participate. The research should attempt to establish what the perceived and real barriers to performing screening were from a primary care perspective, and what adaptations could be made to make the task of screening more acceptable.

In the past in Bradford, multiple initiatives have been performed to increase public awareness of, education about, and testing for viral hepatitis in migrants. In 2008, a large community

study was conducted in mosques and community centres in Bradford, offering testing for viral hepatitis to people of south Asian origin (296). Although only an anecdotal observation, it is interesting that the majority of staff and clinicians within the practices approached by the HepFree research team were of south Asian origin. Yet, despite this, engagement rates by GPs in the trial were low.

These findings might suggest that case identification of viral hepatitis in immigrant populations is still not a priority, furthermore, given that these are the observations in an area of England that is densely populated with migrants, it would be reasonable to speculate that implementing a widespread screening programme for viral hepatitis in primary care in areas of England with lower numbers of immigrant populations would be even more challenging.

Conversely however, the obstacles encountered in trying to engage practices and set up HepFree may be related to the fact that HepFree was a research trial and not an established screening programme. Following discussions with clinicians, it was evident that practices feel adequately equipped to facilitate pre-existing NHS preventative screening programmes. This is because although the practical procedure is performed by a member of staff at the practice, for which they are reimbursed, all reporting of results and subsequent referrals to secondary care is done by a central body. Clinicians within practices are notified of the outcomes of screening tests but are not expected to initiate the pathway for assessment and treatment if required.

The HepFree trial as described in Methods and Materials was considerably more labour intensive, with practices responsible for performing the searches on S1 to identify potentially eligible participants, generating and distributing the invitation letters, booking the appointments, performing consent and collecting the blood samples for analysis as well as reviewing all test results and notifying the trial team in the event of a positive result. It may therefore be feasible to reproduce HepFree on a larger scale, and lead to greater engagement by practices if changes were made to HepFree to make the work load more closely resemble other established preventative screening strategies both in terms of the way individuals are invited, the way results are reported and follow-up arrangements made.

4. HepFree results: Participant eligibility.

4.1 Introduction

One of the objectives of the HepFree trial was to assess the feasibility of accessing and using pre-existing medical records in GP surgeries in primary care to identify individuals at risk of viral hepatitis based on their demographics, including country of birth, ethnicity and main spoken language. In this chapter I will present the results of the eligibility searches that were designed and created to identify 'high-risk' individuals based on pre-existing Read codes contained within individual patient electronic medical records.

As discussed in Materials and Methods, I was responsible for designing and helping to build the electronic searches that were uploaded and published onto the clinical computer systems in primary care, with the help of the data quality team at the Yorkshire and Humber Commissioning Support Unit, Douglas Mill, Bowling Old Lane, Bradford, West Yorkshire, BD5 7JR.

In this chapter I will present eligibility data from ten of the eighteen practices that were performing targeted testing as part of the HepFree trial that had completed eighteen months of testing by February 2016, when data for this thesis was collated. This chapter does not include any data obtained from control practices. The reason for this is that at the time of writing this thesis the HepFree study was incomplete and therefore data from control practices had not been analysed.

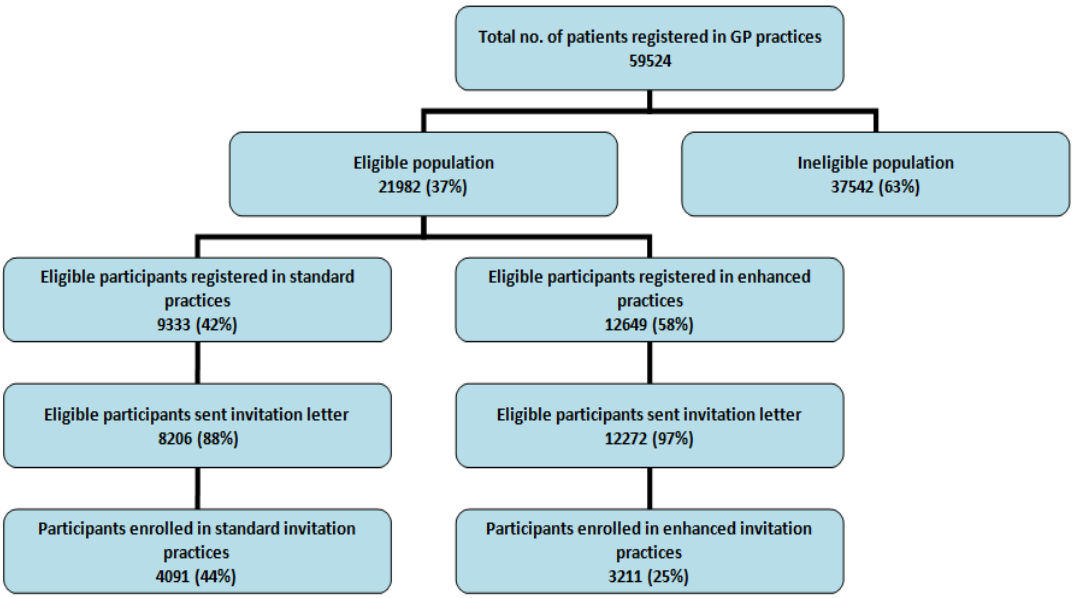
In subsequent chapters, analysis of data from participants that both consented to participate and declined the offer of testing in these practices will be presented.

4.2 Results

As outlined in Materials and Methods, data were analysed by IBM SPSS statistics 23 and Microsoft EXCEL.

In the ten practices that had completed targeted testing for HepFree, the potential study participant population consisted of 21,982 individuals, of which 20,478 (93%) were sent an invitation letter. In total 7,302 participants were recruited and underwent testing for viral hepatitis, accounting for 35.7% of the potential study participant population. Figure 16 is a summary of targeted testing activity in the ten practices included in the analysis.

Figure 16: A summary of participant recruitment in targeted testing practices based in Bradford



A flow chart summarising trial recruitment in GP surgeries that were randomised to perform targeted testing in Bradford and included in this analysis. From an eligible population of 21,982, 7302 individuals attended for testing, representing an uptake rate of 33.2%. Targeted testing was performed more frequently in practices randomised to send standard invitation letters, 44% compared to those sending enhanced invitation letters, 25%.

As discussed within Materials and Methods, at the time of the SIV practices were instructed to generate and send by second class mail, a modified and personalised trial invitation letter. Letters were modified to include the practice name and contact details that could be used to book an appointment to attend for screening. Administrative staff were advised to send a letter to all potential study participants registered at the practice. A potential study participant, also referred to as an eligible individual, was anyone registered at a practice assigned to perform targeted testing that fulfilled the trial inclusion criteria (see Methods). Study participants were identified using eligibility searches that had been created and published on S1 units.

One of the trial objectives was to establish the feasibility of integrating targeted testing for viral hepatitis into primary care, and therefore the trial protocol stipulated that all trial related activities, including the distribution of invitation letters were to be performed by staff within the practice, without additional input from the research team. From an eligible population of 21, 982, 93% were sent an invitation letter. From discussions with practices, staff shortages related to long-term sickness in addition to full-time vacancies and the demands of pre-existing practice work were three of the main obstacles that prevented invitation letters from being distributed and resulted in non-contact of 7% of potential study participants.

4.2.1 Demographics of the eligible population

The results of the eligibility searches conducted to identify potential study participants in each of the targeted testing practices are set out in Tables 9-11 and Figures 17-19. In each of the Tables, the number of potential study participants (eligible participants) is expressed as a percent of the total potential study population and as a percent of the total number of patients (both eligible and ineligible) registered in all ten HepFree practices included in this thesis.

Table 9: The demographics of the HepFree potential study population

The countries of origin of all potential study participants registered and eligible to be invited for testing in HepFree practices. Data are expressed as a total number, percent of the total eligible HepFree population and as a percent of all patients registered in Bradford practices performing HepFree (eligible and ineligible).

Country of origin	No. of eligible participants	Percent of total eligible population	Percent of all patients in HepFree practices
Africa	358	1.6	0.6
Asia-Pacific	7415	33.7	12.5
Eastern Europe	1737	7.9	2.9
Latin America & Caribbean	79	0.4	0.1
Western Europe & others	2298	10.5	3.9
Not known	10095	45.9	17.0
TOTAL	**21982**	**100.0**	**36.9**

Table 10: The demographics of the HepFree potential study population

The main spoken languages where available, of all potential study participants registered and eligible to be invited for testing in HepFree practices. Data are expressed as a total number, percent of the total eligible HepFree population and as a percent of all patients registered in Bradford practices performing HepFree (eligible and ineligible).

Main spoken language	No. of eligible participants	Percent of total eligible population	Percent of all patients in HepFree practices
English	1958	8.9	3.3
Urdu/Punjabi	9278	42.2	15.6
Gujurati	381	1.7	0.6
Polish	923	4.2	1.6
Bengali	925	4.2	1.6
Others	2362	10.7	4.0
Not known	6155	28.0	10.3
TOTAL	**21982**	**100.0**	**36.9**

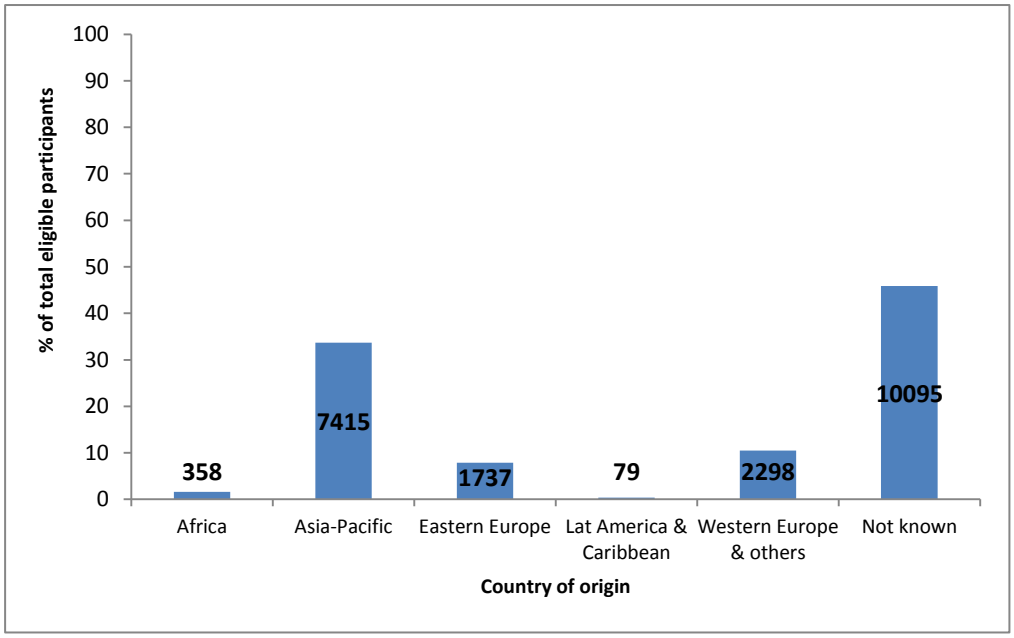
Table 11: The demographics of the HepFree potential study population

The recorded ethnicities of all potential study participants registered and eligible to be invited for testing in HepFree practices, where available. Data are expressed as a total number, percent of the total eligible HepFree population and as a percent of all patients registered in Bradford practices performing HepFree (eligible and ineligible).

Ethnic group	No. of eligible participants	Percent of total eligible population	Percent of all patients in HepFree practices
White	1457	6.6	2.4
Mixed/Multiple ethnic groups	260	1.2	0.4
Asian/British Asian	17556	79.9	29.5
Black: African/Caribbean/ British	655	3.0	1.1
Other ethnic group	1055	4.8	1.8
Not known	999	4.5	1.7
TOTAL	**21982**	**100**	**36.9**

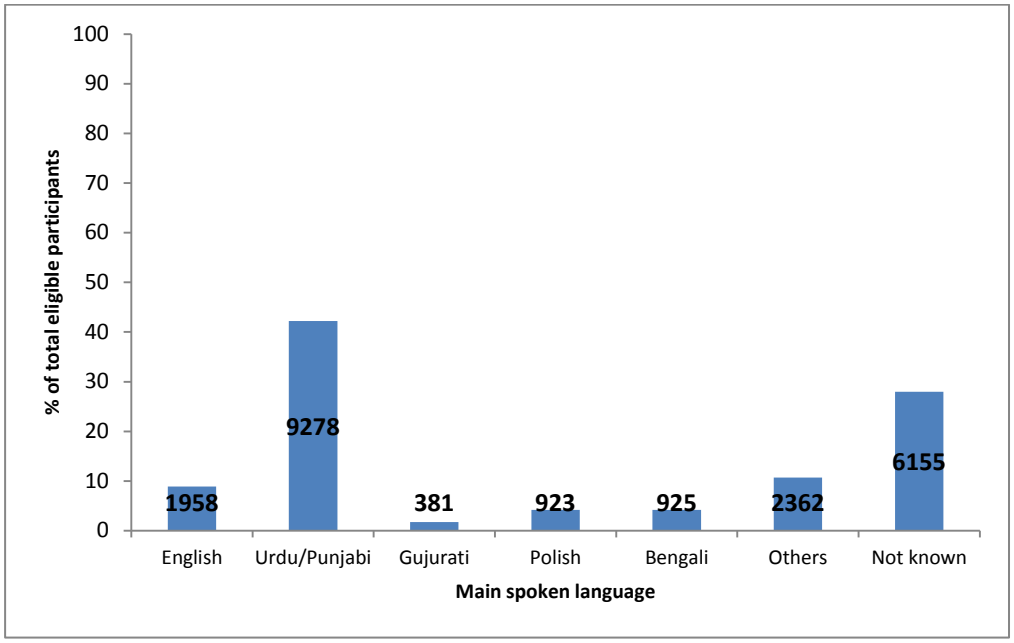
Figure 17: The demographics of the HepFree potential study population

The numbers on the bars represent the number of participants eligible for testing within each category.



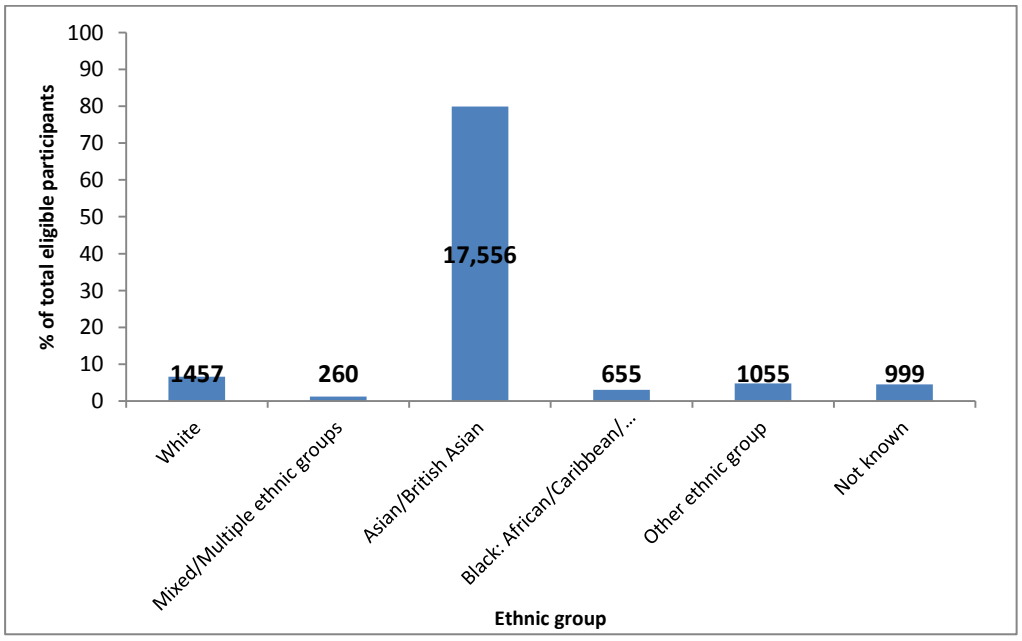
A column chart summarising the countries of origin of all potential study participants registered in GP surgeries recruited to perform targeted testing in the HepFree trial. In 46% of cases, due to deficiencies in data collection in primary care, the country of origin of individuals was not known.

Figure 18: The demographics of the HepFree potential study population



A column chart summarising the main spoken languages of all potential study participants registered in GP surgeries recruited to perform targeted testing in the HepFree trial. In Bradford, Urdu/Punjabi was most frequently documented as the main spoken language in the potential study population. This finding is in keeping with the majority of potential study participants originating from countries within Asia-Pacific.

Figure 19: The demographics of the HepFree potential study population



A column chart summarising the ethnicity of all potential study participants registered in GP surgeries recruited to perform targeted testing in the HepFree trial. 80% of potential study participants were Asian/British Asian.

As described in Materials and Methods, the eligibility searches identified individuals registered within each practice that had one or more of the pre-selected Read codes in their medical record that suggested that they originated from an area of high-risk for viral hepatitis but had not previously been tested, or given a formal diagnosis of hepatitis. Table 12 illustrates the total number of individuals eligible to participate in the ten HepFree practices, broken down by ethnicity. Data are expressed as a percent of the total number of patients registered within the same practices and compared with data collected in the 2011 census for Bradford. The overall percentage figures for the two classifications are 36.9% (HepFree) and 35.6% (census). This shows that the two groups are similar, with small differences likely to represent changes in patterns of migration in the time since the last census was performed. From this analysis it can be assumed that the sample invited for testing in the HepFree practices is representative of the wider population in Bradford.

Table 12: The ethnicity of potential HepFree study participants compared to Bradford census data

The documented ethnicity of individuals identified as eligible to participate from HepFree search results. Data are expressed as a percent of the total number of patients registered within the HepFree practices (eligible and ineligible) and compared with the 2011 census for Bradford.

Ethnic group	No. of eligible participants	Percent of all patients in HepFree practices	Percent of respondents 2011 census data
White (other)	1457	2.4	3.0
Mixed/Multiple ethnic groups	260	0.4	2.5
Asian/British Asian	17556	29.5	26.8
Black: African/Caribbean/ British	655	1.1	1.8
Other ethnic group	1055	1.8	1.5
Not known	999	1.7	
Total	**21,982**	**36.9**	**35.6**

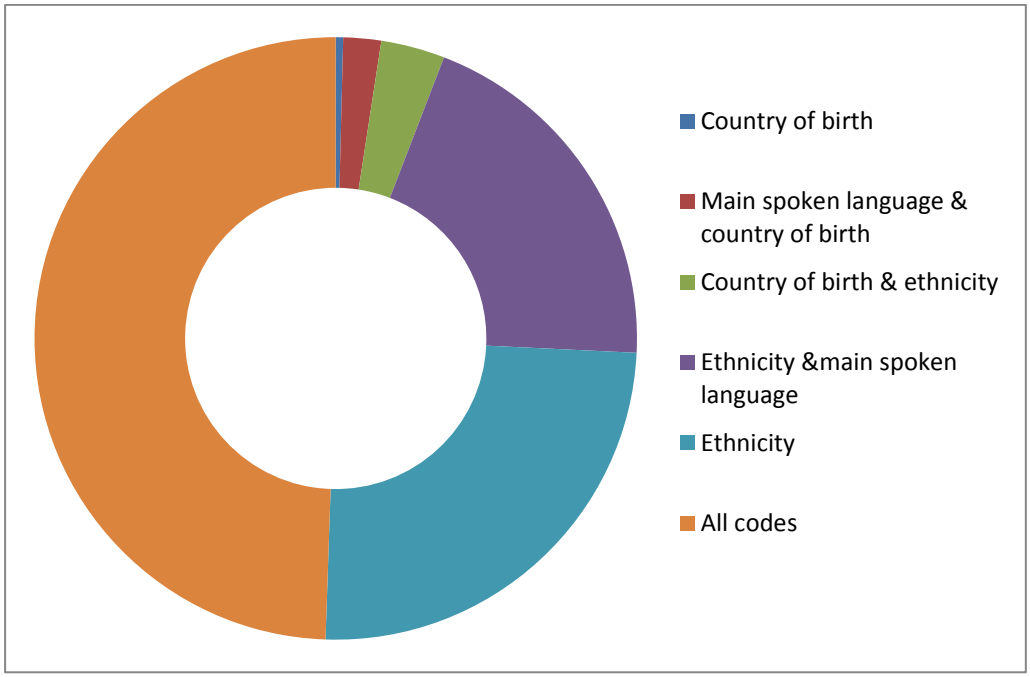
In the ten practices from which data were collated for this thesis, a total of 59, 524 patients were registered. The eligibility searches identified that 21,982 (36.9%) were potential study participants, therefore the remaining 37,542 (63.1%) patients were considered ineligible for participation in HepFree.

The doughnut diagram (Figure 20) demonstrates the combinations of Read codes that potential study participants were identified by in the eligibility searches. In 48.4% of cases, electronic patient records were comprehensively completed and contained Read codes pertaining to all search criteria; ethnic group, country of origin and main spoken language. The demographic field for country of birth was completed least efficiently, with an absent field in 45.9% of records. In these cases it was not possible to establish whether the potential study participant was a first or second generation immigrant.

The results of the eligibility searches highlighted inconsistencies in demographic data collection and recording in primary care. The results of the searches further demonstrated that in order to identify individuals at risk of viral hepatitis by using pre-existing databases, searches needed to be sophisticated enough to be able to identify an individual using several demographic categories.

Within the Bradford cohort of GP practices, the ethnic category with the largest number of potential study participants was Asian/British Asian. Black African/Caribbean/British individuals were represented least in the population sample.

Figure 20: Read code combinations within electronic medical records of eligible participants in HepFree practices



The combinations of Read codes contained within the electronic medical records of eligible participants in HepFree practices. In 48.4% of cases, electronic patient records were comprehensively completed and contained Read codes pertaining to all search criteria; ethnic group, country of origin and main spoken language (orange).

Because ethnicity was the most comprehensively filled demographic field, Table 13 summarises potential HepFree trial participants registered in each GP practice by ethnicity. In the table, the number of eligible participants in each ethnic group is expressed as a number, as a percent of the total study population (also known as eligible population) and as a percent of the total patient population within each practice (also known as list size).

Table 13: The ethnicity of eligible HepFree participants in Bradford

Ethnicity data obtained through SystmOne from each practice recruited to the study. The list size (total number of patients registered at the practice) as well as number of eligible study participants in each practice is included. For each ethnic group of interest, the number of individuals registered at each practice is stated and data expressed as a percent of the total number of eligible participants within the practice as well as a percent of all of patients registered (list size).

			White			Mixed/Multiple			Asian/Brit Asian			Black			Other & Unknown		
Practice	List size	Total No. of eligible participants	No.	% of eligible	% of total list	No.	% of eligible	% of total list	No.	% of eligible	% of total list	No.	% of eligible	% of total list	No.	% of eligible	% of total list
1	5461	3539	190	5.4	3.5	12	0.3	0.2	3147	88.9	57.6	37	1.0	0.7	153	4.3	2.8
2	5080	3237	110	3.4	2.2	38	1.2	0.7	2700	83.4	53.1	54	1.7	1.1	335	10.3	6.6
3	6191	1942	77	4.0	1.2	29	1.5	0.5	1659	85.4	26.8	70	3.6	1.1	107	5.5	1.7
4	4119	2557	105	4.1	2.5	11	0.4	0.3	2324	91.0	56.4	33	1.3	0.8	84	3.2	2.0
5	4840	2384	397	16.7	8.2	19	0.8	0.4	1436	60.2	31.7	36	1.5	0.7	496	20.8	10.2
6	6399	3170	38	1.2	0.6	21	0.7	0.3	2913	91.9	45.5	25	0.8	0.4	173	5.5	2.7
7	7401	685	45	6.6	0.6	36	5.3	0.5	475	69.3	6.4	58	8.5	0.8	71	10.4	1.0
8	7114	945	138	14.6	1.9	33	3.5	0.5	506	53.5	7.1	102	10.8	1.4	166	17.6	2.3
9	8778	1182	305	25.8	3.5	41	3.5	0.5	577	48.8	6.6	86	7.3	1.0	173	14.6	2.0
10	4141	2341	52	2.2	1.3	20	0.9	0.5	1819	77.7	43.9	154	6.6	3.7	296	12.6	7.1
TOTAL	59524	21982	1457	6.6	2.4	260	1.2	0.4	17556	79.9	29.5	655	3.0	1.1	2054	9.3	3.5
Abbreviations **Asian/Brit**: Asian & British Asian, **Black**: Black African/Caribbean/ British																	

In Bradford, irrespective of postcode district, the greatest proportion of potential study participants in each GP practice were of Asian/British Asian ethnicity, ranging from 48.8% of potential participants in practice 9 to 91.9% of the potential study population in practice 6.

Table 14 provides a summary of the populations tested in each HepFree practice by ethnicity.

Table 14: The ethnicity of HepFree study participants in Bradford

Data on the ethnicity of participants recruited to the HepFree trial in Bradford. For each practice performing targeted testing that is included in this analysis, the number of individuals from each ethnic group that participated is expressed as a percentage of the number of individuals that were eligible to participate.

	White		Mixed/Multiple		Asian/Brit Asian		Black		Other & Unknown		**TOTAL**	
Practice	No. eligible	No. tested (%)	No. eligible	No. tested (%)	No. eligible	No. tested (%)	No. eligible	No. tested (%)	No. eligible	No. tested (%)	No. tested	No. eligible population per practice (%)
1	190	76 (40.0)	12	4 (33.3)	3147	1551 (49.3)	37	20 (54.0)	153	26 (17.0)	1677	47.4
2	110	46 (41.8)	38	23 (60.5)	2700	1744 (64.6)	54	24 (46.2)	335	64 (19.1)	1901	58.7
3	77	28 (36.3)	29	13 (44.8)	1659	838 (50.5)	70	26 (37.1)	107	32 (30.0)	937	48.2
4	105	12 (11.4)	11	0 (0.0)	2324	486 (20.9)	33	3 (9.1)	84	12 (14.3)	513	20.1
5	397	181 (45.6)	19	9 (47.4)	1436	852 (59.3)	36	23 (63.9)	496	28 (5.6)	1093	45.8
6	38	7 (18.4)	21	2 (28.6)	2913	516 (17.7)	25	2 (8.0)	173	2 (1.2)	529	16.7
7	45	9 (20)	36	4 (11.1)	475	47 (9.9)	58	4 (6.9)	71	8 (11.3)	72	10.5
8	138	13 (9.4)	33	3 (9.1)	506	44 (8.7)	102	7 (6.9)	166	1 (0.6)	68	7.2
9	305	35 (11.5)	41	7 (17.1)	577	94 (16.3)	86	14 (16.3)	173	4 (2.3)	154	13.0
10	52	4 (7.7)	20	2 (10.0)	1819	331 (18.2)	154	16 (10.4)	296	5 (1.7)	358	15.3
TOTAL	1457	411 (28.2)	260	67 (25.8)	17556	6503 (37.0)	655	139 (21.2)	2054	182 (8.9)	7302	33.2

Abbreviations
(%): Percent of the eligible population by ethnic group in each practice who attended for testing

Trial participation was highest amongst individuals of Asian/British Asian ethnicity, with 37.0% of all potential study participants consented for testing belonging to this ethnic group. In contrast, trial participation was lowest in individuals that had no documented country of birth. This finding may be indicative of a communication barrier between the practice and this group of individuals, preventing both demographic data from being collected and preventing discussions about the trial from being conducted. Alternatively this finding may reflect a global lack of engagement from this group of individuals with primary care services.

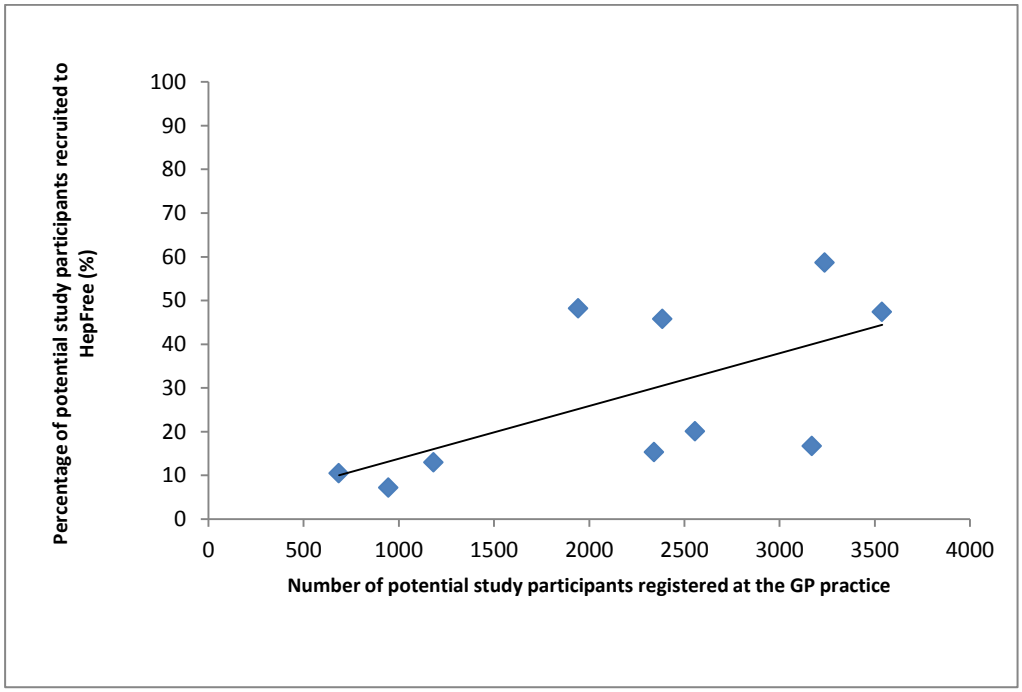
In order to explore whether the size of the potential study participant population, and the total number of patients registered at each practice (practice list size) had an impact on case-finding performance, a comparison was made between the total number of patients registered at each practice (practice list size), the number of individuals identified as potential study participants from the trial searches and total number of participants tested at each practice (Table 15 and Figures 21 and 22).

Table 15: HepFree recruitment data in per GP surgery in Bradford

Data on the number of patients registered at each practice (list size), the number of potential study participants registered and the number recruited to participate in the study.

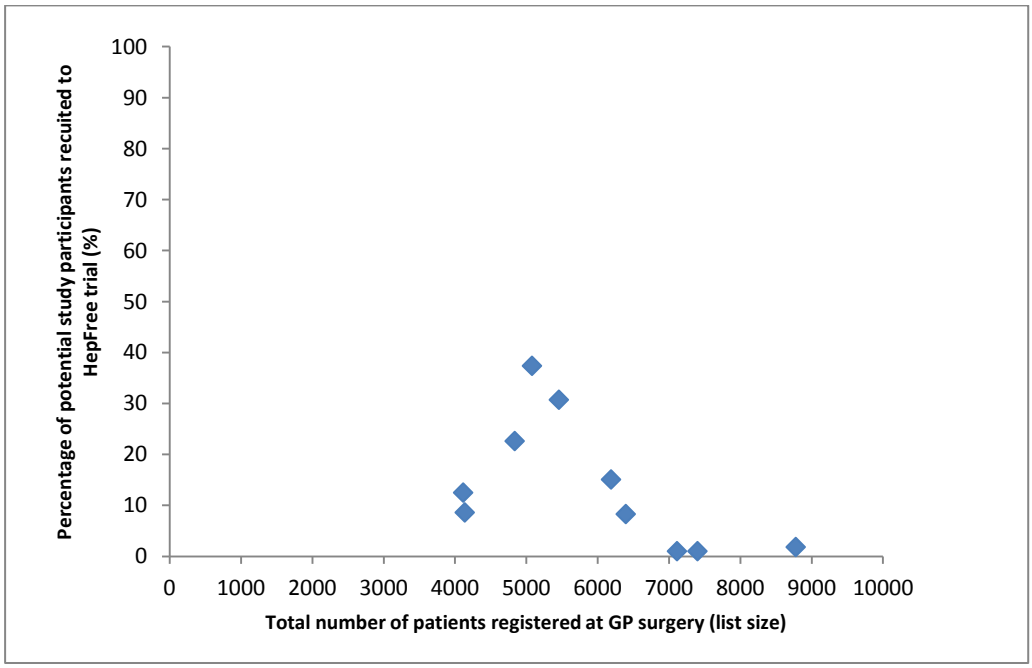
Practice	List size	No. of potential study participants registered	No. of potential participants recruited	No. recruited as a percent of total potential study participants	No. recruited as a percent of total list size
1	5461	3539	1677	47.4	30.7
2	5080	3237	1901	58.7	37.4
3	6191	1942	937	48.2	15.1
4	4119	2557	513	20.1	12.5
5	4840	2384	1093	45.8	22.6
6	6399	3170	529	16.7	8.3
7	7401	685	72	10.5	1.0
8	7114	945	68	7.2	1.0
9	8778	1182	154	13.0	1.8
10	4141	2341	358	15.3	8.6
TOTAL		21,982	7,302		

Figure 21: A scatter plot of potential study participants per GP practice and participant recruitment to HepFree.



A scatter plot of the relationship between the number of potential study participants registered at a HepFree practice performing targeted screening (x-axis) and the percentage of potential study participants subsequently recruited to the HepFree trial (y-axis). A non-significant positive correlation was identified between the number of potential study participants registered at each practice and testing performance, Pearson correlation coefficient, $r = 0.6236$, $n = 10$, $p = 0.054$.

Figure 22: A scatter plot of practice list size and participant recruitment to HepFree.



A scatter plot of the relationship between GP practice size (x-axis) and the percentage of potential study participants recruited to the HepFree trial (y-axis). No correlation was demonstrated between practice list size and testing activity in HepFree. Targeted testing was performed least frequently in practices with the largest numbers of patients registered. Pearson correlation coefficient, r = -0.4214, n = 10, p = 0.225.

Discussion

Two of the objectives of the HepFree trial were to assess the feasibility of using information stored in electronic medical records in GPs in primary care in order to identify individuals at risk of viral hepatitis, and secondly to explore whether practices would be able to implement a case-finding programme for viral hepatitis in 'high-risk' populations registered within their practices.

As discussed within chapter three, although recruitment of the required number of practices was eventually completed, persuading GPs to adopt HepFree was often difficult with multiple obstacles encountered that needed to be overcome. The methods and procedures used to contact, recruit and finally initiate practices varied greatly, usually because the trial team encountered a myriad of different logistical difficulties in each of the practices approached.

On reflection, it is possible that some of the obstacles that we encountered when trying to engage practices occurred as a result of the fact that HepFree was a research trial. Despite the main objective of the trial being to test 'at-risk' populations to detect potentially curable diseases, in the current financial climate with budget cuts, GP practices may have been wary of additional costs associated with viral hepatitis testing in their practice population. Although the study provided financial re-imbursement for both trial administrative duties in addition to allied healthcare professionals time used for trial related visits as well as the cost of the blood test, we did not take into account the financial impact of either the additional appointment required for a clinician to discuss the results with a patient in the event of a positive result, or the cost of both the new-patient referral and all subsequent follow-up visits.

Concerns of a similar nature were raised by clinicians in primary care when approached and asked about providing targeted testing for viral hepatitis in immigrant populations in a qualitative research project performed prior to HepFree commencing by Sweeney et al (327). Following discussions with local clinicians, the reason why practices are able to facilitate NHS preventative screening programmes is that although the procedure is performed by a member of staff at the practice, for which they are reimbursed, all reporting of results and subsequent referrals to secondary care is performed by a central body, it does not add to the work-load of the individual practice. It may therefore be feasible to reproduce HepFree on a larger scale, with greater engagement from GPs if changes were made to the methodology, in

particular the way that positive test results were reported both to the practice and to the patient. One option may be to explore employing and training a team of 'specialist nurses' whose role would be to process results, inform individuals of positive results and organise on-going management when required.

In the ten practices performing targeted testing from which data were collated for this thesis, a total of 59, 524 patients were registered, of which 21, 982 (36.9%) individuals were identified as being eligible to participate in targeted testing, the remaining 37, 542 (63.1%) patients were not eligible for HepFree. As discussed previously, these figures, when compared to ethnicity data provided by respondents to the 2011 census demonstrate that the practices selected to perform HepFree were very typical of the ethnic makeup of Bradford. In the 2011 census, White British/Irish and Gypsy Irish traveller represented 64.43% of the total respondents, with 35.57% made up of Other White, Asian/British Asian, Black/Black British, mixed or other ethnic groups (Table 12).

In the practices recruited to perform HepFree, trial specific searches were used to identify potential study participants from the total list of patients registered. Participants were identified by Read codes that had previously been recorded in their electronic records. The results of these searches demonstrated that the demographic field denoting ethnicity was completed most comprehensively, with only 4.5% of potential study participants that were identified from another demographic Read code having an absent field for ethnicity.

Historically, within primary care, financial incentives were provided in return for recording of ethnicity data through the Quality and Outcomes Framework (QOF) and this resulted in dramatically increased recording to levels of over 90% for all newly registered patients (328). The results from our eligibility searches for HepFree support this data and confirm the high rate of recording of ethnicity data. In their study, Mathur et al also investigated the quality and accuracy of ethnicity data recorded in primary care. In this study, ethnicity data obtained from primary care was compared with data collected and stored by secondary care. In 85% of cases, ethnicity data was consistent across both databases however discrepancies were identified more frequently in data recording in ethnic minority patients. Validation of ethnicity data could be performed by using name recognition software such as Onomap or Nam Penchan. These software programmes are not completely accurate though as they cannot account for ethnic mixing and inter-racial marriage, both of which result in surname

changes. In HepFree we did not develop a method for validating the results obtained from the eligibility searches.

The relationships between the sizes of the potential study participant populations in each practice versus targeted testing performance as well as practice list size versus targeted testing performance were examined in Table 15 and Figures 21 and 22. A non-significant positive correlation was identified between the number of potential study participants registered at each practice and testing performance (Figure 21). For the two variables list size and testing performance, a negative correlation was demonstrated (Figure 22).

In practices with small numbers of potential study participants, recruitment and testing rates were particularly low (practices 7, 8 and 9). The opposite was observed in practices with large numbers of eligible individuals registered; in these practices testing was performed on a greater scale (practices 1, 2 and 5). One possible explanation for the patterns observed is that practices with large numbers of potential study participants encountered their target population more frequently in a clinical setting and were therefore able to offer testing opportunistically compared to practices with small numbers of potential study participants. Another explanation may be that in the practices with smaller numbers of eligible participants registered, practice staff were not encountering potential study participants very frequently so they may have felt less familiar with trial recruitment procedures and less equipped to deal with potential questions from participants that were being offered the viral hepatitis test and therefore were reluctant to offer testing opportunistically.

Although no correlation was demonstrated between practice list size and testing activity in HepFree (Figure 22), the scatter plot demonstrates that targeted testing activity was lowest in practices with the largest numbers of patients registered (eligible and ineligible). These practices may have performed inferiorly in terms of trial recruitment due to an increased work load generated by a large patient population. An alternative explanation for trial recruitment performance in practices with large populations is that potential study participants encountered difficulties when attempting to obtain an appointment for testing due to high demand on practice resources.

In order to determine why some practices were more effective in engaging patients than others, once the targeted testing element of the HepFree trial has been completed at all sites

in England, a qualitative sub-study will commence. Here, various members of staff from within practices that have performed trial related activities as part of HepFree will be invited to participate in interviews aimed at assessing attitudes towards case-finding for viral hepatitis in primary care. In addition to data obtained from these semi-structured interviews, baseline data including practice staff to patient ratios, staff to room ratios, participant recruitment levels and the presence of onsite phlebotomy services will be collected. The researchers will attempt to explore the motivations and challenges of running a screening programme in primary care as well as any practical obstacles encountered.

Previous research has attempted to understand factors that both hinder and promote the uptake of complex interventional trials, like HepFree by GPs and have attempted to understand variations observed in testing performance observed in these trials (329). In a retrospective analysis of performance by practices participating in a complex intervention trial that introduced rapid HIV testing to patients in primary care, the diffusion innovations model developed by Greenhalgh et al, was used. This model is widely recognised, providing a framework for analysing implementation processes (330). The authors identified five aspects of the model that explained the performances observed in practices participating in the HIV 'screening' trial. These five aspects were, system antecedents for innovation, system readiness for innovation, adopter characteristics, implementation process and, reinvention and local customisation. In the HIV trial, high-recruiting practices were often innovative, characterised by strong leadership, good managerial relations, a readiness for change and that had time available to implement new processes. Furthermore, staff within these practices believed in the beneficial value of performing the intervention and were confident in the procedures required to perform testing. In this trial, a positive test result appeared to reinforce staff commitment to participant recruitment. The opposite was observed in practices with poor testing performances. Here, less effective managerial relations were observed and time constraints preventing practices from engaging fully with the trial resulted in a lack of familiarity with testing procedures (329). Performing a retrospective analysis of high and low performers in HepFree will provide invaluable information prior to widespread implementation of a screening programme for viral hepatitis, if the final trial results support this.

From analysis of HepFree data, it was evident that participation in testing varied between participants of different ethnicities (Table 15). The highest proportion of respondents to the study were of Asian/British Asian ethnicity, 37%, compared to 8.9% in individuals with either no documented ethnicity or no meaningful ethnicity recorded. The absent field denoting

ethnicity may be a surrogate marker reflecting a global lack of engagement between this group of individuals and primary care services.

Non-engagement in testing may be the result of linguistic and/or literacy barriers, access to healthcare 'user ignorance' or due to cultural perceptions and stigma relating to a diagnosis of viral hepatitis. In qualitative research performed using focus groups that helped to inform the trial design of HepFree by Sweeney et al, several barriers were identified that would prevent engagement by individuals with a primary care based screening programme. These barriers included a lack of knowledge about the disease been tested for, language and communication barriers, limited time to attend for testing, lack of adequate social support to deal with a positive diagnosis and low levels of trust and confidence in general practice based care (327). Interestingly in the focus group interviews, although key informants from the Pakistani and Chinese communities expressed that individuals with a family member that had been affected by hepatitis would have increased awareness of the conditions been tested for, they felt that this group still lacked specific knowledge relating to viral hepatitis. In this focus group, key informants from Eastern European and African communities demonstrated very low levels of understanding relating to viral hepatitis (327).

In order to explore in more detail, factors that impact on an individual's decision to engage with testing, a sub-study by Owiti et al was designed and conducted in conjunction with the HepFree trial. In this sub-study, potential study participants were contacted by a member of the research team prior to being invited for testing to collect information on attitudes as well as perceived barriers towards testing for viral hepatitis. This research was performed via semi structured interview over the telephone using a population-based survey of knowledge of viral hepatitis in conjunction with other questionnaires including Patient Health Questionnaire (PHQ-9) and the Generalised Anxiety Disorder 7-item (GAD-7) questionnaire.

5. HepFree results: Recruitment and targeted testing outcomes

5.1 Introduction

In this chapter, demographic data from both the eligibility searches that were conducted to identify potential study participants, as well as data collected in the trial-specific template completed at the time of testing will be analysed to in order to gain information on the demography of individuals that engaged with our case-finding programme. Within the cohort of individuals that consented for testing through HepFree, I will initially explore the methods of engagement that were used by practices to recruit participants as well as investigate factors associated with trial participation.

5.2 Results

In targeted testing practices that were included in the analysis, 7,302 individuals were recruited, consented and underwent testing for viral hepatitis. This figure represents 35.7% of the potential study participant population that received an invitation letter to participate in the trial.

The population that engaged with the study consisted of 4173 females (57.1%), median age 39 (IQR 30); and 3123 males (42.8%), median age 43 (IQR 33). The gender of 6 participants was not known (0.1%). A chi-square test performed to examine the relationship between gender and testing was highly significant X^2 (1) = 155.651, p <.0001 identifying that females were more likely to attend for testing compared to males.

Table 16 summarises the characteristics of the eligible population, with information obtained from the eligibility searches, compared to characteristic of individuals that were recruited to HepFree.

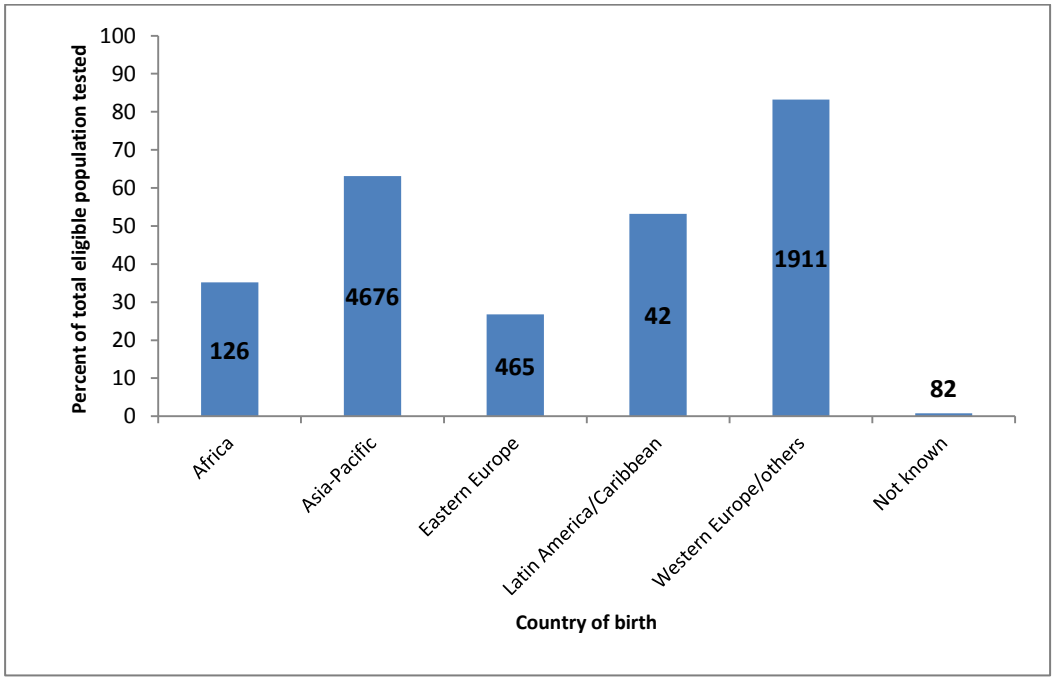
Table 16: Characteristics of potential study participants and individuals recruited to HepFree.

The characteristics of the eligible study population registered in HepFree practices compared to the characteristics of individuals that consented to participate in the trial. Data obtained from SystmOne.

	Potential study participants	Consented Participants (%)
Gender		
Male	10719	3123 (29.1)
Female	11256	4173 (37.1)
Not known	7	6
Generation		
First	9589	5319(55.5)
Second	2298	1875(81.6)
Not known	10095	108 (1.1)
Median age (IQR)		
Male	36 (28)	43 (33)
Female	35 (27)	39 (30)
Not Known	47 (35)	42.5 (33.5)
Age groups		
18-29	6862	1434 (20.9)
30-39	6200	1941 (31.3)
40-49	4122	1693 (41.1)
50-59	2130	995 (46.7)
60-69	1439	707 (49.1)
70+	1229	532 (43.3)
Ethnic group		
White	1457	411 (28.2)
Mixed	260	67 (25.8)
Asian/British Asian	17556	6503 (37.0)
Black	655	139 (21.2)
Other ethnic group	1055	166 (15.7)
Not known	999	16 (1.6)
Country of birth		
Africa	358	126 (35.2)
Asia-Pacific	7415	4676 (63.1)
Eastern Europe	1737	465 (26.8)
Latin America/Caribbean	79	42 (53.2)
Western Europe/others	2298	1911 (83.2)
Not known	10095	82 (0.8)
Main spoken language		
English	1958	1739 (88.8)
Urdu/Punjabi	9278	4100 (44.2)
Gujurati	381	98 (25.7)
Polish	923	160 (17.3)
Bengali	925	425 (45.9)
Other	2363	648 (27.4)
Not known	6155	132 (2.1)
Abbreviations: **Mixed:** Mixed or multiple ethnicities, **Asian/Brit**: Asian & British Asian, **Black**: Black African/Caribbean/ British		

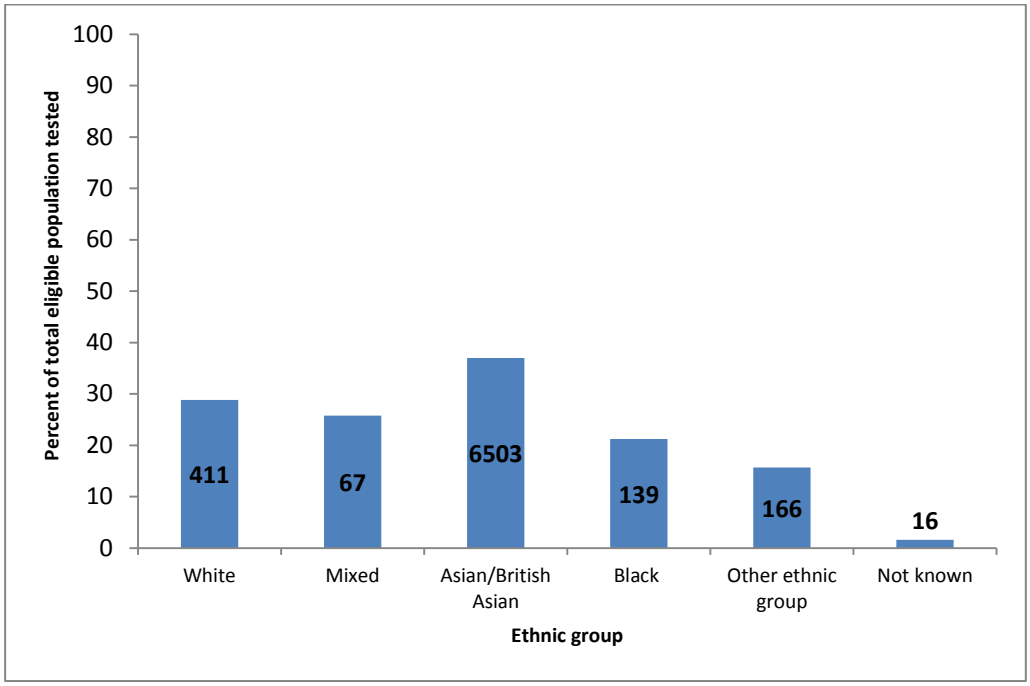
Figures 23-25 demonstrate the countries of birth, ethnic groups and main spoken languages of individuals recruited for viral hepatitis testing through HepFree.

Figure 23: The demographics of individuals recruited to the HepFree trial



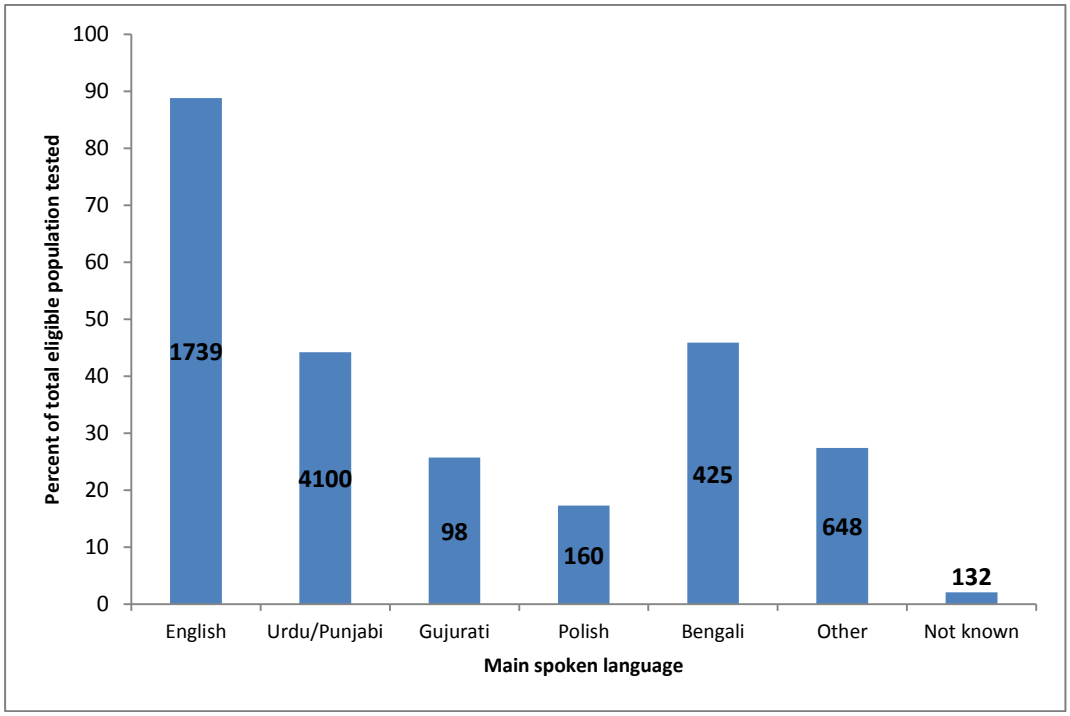
A column chart summarising the countries of origin (x-axis) of individuals recruited and tested for viral hepatitis through the HepFree trial. Data are expressed as both numbers tested (figures on the columns) and as a percent of the total tested population (y-axis). For individuals with a documented country of origin, testing was most frequently conducted in individuals originating from countries within Asia-Pacific (n=4676).

Figure 24: The demographics of individuals recruited to the HepFree trial



A column chart summarising the documented ethnicity (x-axis) of individuals recruited and tested for viral hepatitis through the HepFree trial. Data are expressed as both numbers tested (figures on the columns) and as a percent of the total tested population (y-axis). 37% (n=6503) of individuals recruited and tested through HepFree in Bradford were Asian/British Asian ethnicity.

Figure 25: The demographics of individuals recruited to the HepFree trial



A column chart summarising the documented main spoken language (x-axis) of individuals recruited and tested for viral hepatitis through the HepFree trial. Data are expressed as both numbers tested (figures on the columns) and as a percent of the total tested population (y-axis). In 56.1% of cases, testing was performed in individuals with a main spoken language of Urdu/Punjabi.

5.2.1 Method of engagement

To determine the impact of the invitation letter on trial engagement, we examined the timing of response by individuals to the letter. Invitation letters were generated for 93% of the eligible population by administrative staff within the GP practices (See Materials and Methods). A total of 8,206 standard invitation letters were sent by practices assigned this intervention arm, and 12,272 enhanced invitation letters (additional information leaflet) were sent out by the remaining practices.

5.2.1.1 Assumption

In order to determine whether the invitation letter was responsible for an individual engaging with testing, the following assumption was made: If recruitment into the trial, defined by the presence of a signed consent form and completed electronic template on SystmOne, occurred between days 1-31 from the date the letter was sent, then recruitment was considered to be associated with the invitation letter. Consent taken on the same date that the letter was generated or after 32 days from the date the letter was generated and sent was considered to be as a result of opportunistic recruitment.

In 81.3% of cases, testing occurred as a result of the opportunistic method of recruitment. The median number of days between the letter being sent and recruitment was 51, IQR 169, range 616, mode equal to 0 days. Table 17 summarises the data pertaining to the number of days between the invitation letter been sent and consent to the trial obtained.

Table 17: Duration of time between trial invitation and recruitment

Grouped data demonstrating the time interval between the trial invitation letters being sent and subsequent participant recruitment. Data are expressed as a number and as a percent of the total recruited. In 81.3% of cases, recruitment occurred either on the same day that the letter was generated, or after 32 days, suggesting opportunistic recruitment.

No. of days to consent	Frequency	Percent (%)	Cumulative percent
Day 0*	1759	24.1	24.1
1-31	1364	18.7	42.8
32-61	753	10.3	53.1
62-91	644	8.8	61.9
92-121	464	6.4	68.3
122-151	311	4.3	72.5
>152	2007	27.5	100.0
TOTAL	7302	100.0	
*Letter generated and participant consented on the same day.			

In order to further investigate factors that may be associated with recruitment, we examined the impact of the type of invitation letter received on recruitment outcomes. In the trial, 7,302 individuals were recruited and tested for viral hepatitis; 56.0% (4,091) of these had been invited using the standard invitation letter and 44.0% (3, 211) had been invited using the enhanced invitation letter.

Using the previously stated assumption, in the trial 1,364 participants were recruited and testing performed between days 1- 31 of the invitation letter been sent by the GP practice, and it was this group where we considered that the letter was directly responsible for participant recruitment. Analysis of data from this participant cohort (n= 1,364) suggests that the type of letter received was highly significant in determining whether testing was performed.

952 (29.6%) of the 3,211 individuals that received an enhanced invitation letter consisting of an invitation letter in addition to an information sheet on viral hepatitis, including the consequences of untreated infection, attended for testing between days 1-31 compared to 412 (10.1%) of the 4,091 individuals that were invited using the standard invitation letter that

did not contain the additional information sheet on hepatitis. In summary, individuals that received the enhanced invitation were more likely to participate in testing compared to individuals who received a standard invitation (OR 3.76; 95% CI: 3.31 – 4.27, p<0.0001).

5.2.2 Participant age

In order to establish whether targeted viral hepatitis testing is considered acceptable and accessed by individuals of all ages, participant age was examined. Establishing the prevalence of viral hepatitis in different age groups will also provide information on whether universal screening of all first and second generation immigrants irrespective of age is justified.

The ages of all participants recruited and tested through HepFree is summarised in Table 18. Although the age group with the highest number of individuals tested was 30-39, as a proportion of the total potential study participant population, testing occurred more frequently in adults of advancing age (Table 19).

Table 18: Grouped data on ages of participants recruited to the HepFree trial

Grouped data on ages and genders of individuals recruited to HepFree. Data are expressed as a figure and percent of total number recruited to the trial.

Gender	Age group	No. of participants tested	Percent of total number tested
Male	18-29	516	7.1
	30-39	753	10.3
	40-49	806	11.0
	50-59	466	6.4
	60-69	328	4.5
	>70	254	3.5
	Total	**3123**	**42.8**
Female	18-29	918	12.6
	30-39	1185	16.2
	40-49	886	12.1
	50-59	528	7.2
	60-69	379	5.2
	>70	277	3.8
	Total	**4173**	**57.1**
Gender unknown	18-29	0	0.0
	30-39	3	0.0
	40-49	1	0.0
	50-59	1	0.0
	60-69	0	0.0
	>70	1	0.0
	Total	**6**	**0.1**
Total	18-29	1434	19.6
	30-39	1941	26.6
	40-49	1693	23.2
	50-59	996	13.6
	60-69	707	9.7
	>70	532	7.3
	Total	**7302**	**100.0**

Table 19: HepFree trial recruitment by age group

The number of individuals in each age group recruited to HepFree. Data expressed as a percent of the total number of eligible participants. Trial recruitment was more successful in individual aged 40 and over.

Age group	No. of potential study participants	No. of participants tested	Percent of total potential participants tested
18-29	6862	1434	20.8
30-39	6200	1941	31.3
40-49	4122	1693	41.1
50-59	2130	995	46.7
60-69	1439	707	49.1
>70	1229	532	43.3
TOTAL	21982	7302	

Independent T – tests were performed to examine the mean ages of participants grouped by gender and by generation. Unsurprisingly, individuals that originated from outside the UK and attended for testing (first generation) were older than second generation study participants. The difference in mean ages between the two groups was statistically significant; first generation *(Mean =47.28, SD = 15.499)* and second generation *(Mean =32.66, SD = 9.875), t (3056.378) = 33.767, p ≤ .05, 95% CI 13.769, 15.467*. Cohen's effect size *(d = 1.13)* suggested a moderate to high practical significance.

The mean ages of males and females that participated in testing was also examined. Females attending for testing were younger than males and again the results were statistically significant; males *(Mean =44.89, SD = 15.504)* and females *(Mean =42.69, SD = 15.787), t (5936) = 5.413, p ≤ .05, 95% CI 1.402, 2.994*. Cohen's effect size *(d = .14)* was small in this case, suggesting that the significant result may be due to the degrees of freedom with significant results occurring more frequently when large sample sizes are tested.

Data was further analysed to establish which, if any factors impacted on trial participation. Due to differences in cultural behaviours and beliefs, individuals were analysed according to ethnicity. Due to the relatively low number of non-Asian subjects participating in the trial in

Bradford, a finding that is likely to have occurred as a consequence of the ethnic composition of the community where the HepFree trial was conducted, participants were grouped for analysis as 'Asian' and 'non-Asian'. Participants with no documented ethnicity were excluded from the analysis.

5.2.3 The impact of ethnicity on trial recruitment

5.2.3.1 Asian Ethnicity

Testing themes in the Asian cohort were reflective of testing activity patterns observed in the overall trial. In this ethnic group, a greater number of females were recruited and tested compared to males (Table 20). A chi-square test of independence was significant, rejecting the null hypothesis that gender and trial participation to undergo testing are independent, therefore concluding that there was an association between gender and testing rates; X^2 (1) =140.607, p=<.0001. The odds of females attending for testing were 1.43 times higher than males.

Table 20: Factors influencing the uptake of testing for hepatitis through the HepFree trial: gender

The impact of gender on recruitment to HepFree in individuals of Asian ethnicity.

Gender	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
Female	8987	3704	41.2	1 (ref)	
Male	8565	2796	32.6	.691 (.649-.735)	<.0001
Unknown	4	3			
TOTAL	17556	6503	37.0		

Table 21: Factors influencing the uptake of testing for hepatitis through the HepFree trial: age

The impact of participant age on trial recruitment in individuals of Asian ethnicity. As a percent of the total eligible study population, testing was performed more frequently in all age groups compared to 18-29 year olds. Univariate analysis demonstrated that testing rates were significantly higher in all age groups compared to 18-29 year olds.

Age category	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
18-29	5459	1295	23.7	1 (ref)	
30-39	4848	1713	35.3	1.757 (1.613-1.914)	<.0001
40-49	3321	1507	45.4	2.671 (2.435 – 2.930)	<.0001
50-59	1636	850	52.0	3.477 (3.099 – 3.902)	<.0001
60-69	1251	647	51.7	3.444 (3.033 – 3.912)	<.0001
>70	1041	491	47.2	2.871 (2.504 – 3.291)	<.0001
TOTAL	17556	6503	37.0		

Participation in HepFree was greatest in individuals aged 50 and older; in these age groups, 50.6% of the eligible population were recruited and tested for hepatitis compared to 33.5% of adults aged 18-49. Testing was performed least frequently in individuals aged 18-29 (Table 21). Univariate analysis demonstrated that testing rates were significantly higher in all age groups compared to 18-29 year olds.

In order to investigate whether gender influenced attendance and participation in individuals of different ages, a comparison was made of testing rates by age groups in females and males (Tables 22 &23).

Table 22: Factors influencing the uptake of testing for hepatitis through the HepFree trial: female age

The impact of participant age on trial recruitment in females of Asian ethnicity. In females, increasing age was associated with attendance for viral hepatitis testing through the HepFree trial.

Age group	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
18-29	2792	821	29.4	1 (ref)	
30-39	2527	1043	41.3	1.687 (1.506 – 1.890)	<.0001
40-49	1622	790	48.7	2.28 (2.008 – 2.588)	<.0001
50-59	826	448	54.2	2.845 (2.426 – 3.337)	<.0001
60-69	652	345	52.9	2.698 (2.267 – 3.211)	<.0001
>70	568	257	45.2	1.984 (1.650 – 2.385)	<.0001
TOTAL	8,987	3704	41.2		

Table 23: Factors influencing the uptake of testing for hepatitis through the HepFree trial: male age

The impact of participant age on trial recruitment in males of Asian ethnicity. In males, increasing age was associated with attendance for viral hepatitis testing through the HepFree trial.

Age group	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
18-29	2667	474	17.8	1 (ref)	
30-39	2319	668	28.8	1.872 (1.673 – 2.140)	<.0001
40-49	1699	717	42.2	3.378 (2.942 – 3.879)	<.0001
50-59	809	402	49.7	4.57 (3.856 – 5.416)	<.0001
60-69	599	302	50.4	4.705 (3.897 – 5.680)	<.0001
>70	472	233	49.4	4.510 (3.671 – 5.542)	<.0001
TOTAL	8,565	2796	32.6		

In nearly every age cohort reviewed, in males, testing was performed less frequently compared to females. In individuals of advancing age, testing rates by gender were comparable. These results suggest that the HepFree screening strategy is not effective in engaging males aged between 18-29 in screening, in this age group, less than 20% of the eligible population were recruited.

To establish whether hepatitis testing rates were influenced by an individual's ability to speak English, trial participation by English speakers were compared to non-English speakers.

Table 24: Factors influencing the uptake of testing for hepatitis through the HepFree trial: main spoken language

The impact of main spoken language; English versus non-English on trial recruitment in individuals of Asian ethnicity. A significant positive association was demonstrated between English as a main spoken language and attendance for testing, OR = 11.0135, 95% CI: 9.3653 – 12.9517, p<.0001.

Language	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
English	1698	1526	89.9	1 (ref)	
Other	10902	4864	44.6	.091 (0.077 – 0.107)	<.0001
Unknown	4956	113	2.3	.003 (.002 - .003)	<.0001
TOTAL	17556	6503	37.0		

Analysis of recruitment and hepatitis testing by main spoken language identified that testing was performed less frequently in individuals in whom English was not the main spoken language; 44.6% versus 89.9% in English speakers. There was a significant positive association demonstrated between English as a main spoken language and recruitment to HepFree, OR = 11.0135, 95% CI: 9.3653 – 12.9517, p<.0001 (Table 24).

5.2.3.2 Non- Asian Ethnicity

The same analysis was performed in HepFree participants with a documented ethnic group other than Asian/British Asian.

Table 25: Factors influencing the uptake of testing for hepatitis through the HepFree trial: gender

A table demonstrating the impact of gender on recruitment to HepFree in individuals of non-Asian ethnicity. In this cohort, a greater proportion of females that were invited to participate in HepFree attended for testing compared to males; 25.8% versus 19.6%.

Gender	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
Female	1780	460	25.8	1 (ref)	
Male	1646	322	19.6	.698 (.594 - .820)	<.0001
Unknown	1	1			
TOTAL	3427	783	22.8		

Similar to patterns observed in the analysis of the Asian cohort, there was a significant negative association between male gender and testing rates in individuals of non-Asian ethnicity. The odds of females attending for testing in this cohort were 1.43 times higher than for males, p = <.0001.

As a proportion of the total eligible population, recruitment into HepFree was much lower in individuals of non-Asian ethnicity, compared to Asian ethnicity; 22.8% versus 37.0%. A chi-square test of independence was significant, rejecting the null hypothesis that ethnicity and attendance for viral hepatitis testing were independent, thus concluding that there was an association between Asian ethnicity and attendance for testing as part of the HepFree trial; X^2 (1) =254.216, p=<.0001.

Table 26: Factors influencing the uptake of testing for hepatitis through the HepFree trial: age

The impact of participant age on trial recruitment in individuals of non-Asian ethnicity. As a proportion of the total eligible study population, testing was performed more frequently in all age groups compared to 18-29 year olds. Univariate analysis demonstrated that testing rates were significantly higher in all age groups compared to 18-29 year olds.

Age group	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
18-29	1051	135	12.8	1 (ref)	
30-39	1005	226	22.5	1.971 (1.560 – 2.49)	<.0001
40-49	640	182	28.4	2.696 (2.101 – 3.46)	<.0001
50-59	416	142	34.1	3.516 (2.680 – 4.613)	<.0001
60-69	160	58	36.3	3.858 (2.666 – 5.583)	<.0001
>70	155	40	25.8	2.360 (1.578 – 3.530)	<.0001
TOTAL	3,427	783	22.8		

Lower rates of attendance for hepatitis testing were observed in all age groups of non-Asian individuals compared to individuals of Asian ethnicity (Table 26). Although slightly higher testing rates were observed in participants of advancing age, only 32.8% of all eligible participants aged 50 and above participated in the trial. As was observed in the Asian cohort there was a negative association between youth and attendance for hepatitis testing, OR = 0.516, 95% CI = 0.43-0.61, P= <.0001.

Table 27: Factors influencing the uptake of testing for hepatitis through the HepFree trial: female age

A table investigating the impact of participant age on trial recruitment in females of non-Asian ethnicity. In this population, increasing age was associated with attendance for viral hepatitis testing through the HepFree trial.

Age group	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
18-29	595	95	16.0	1 (ref)	
30-39	512	140	27.3	1.981 (1.478 – 2.655)	<.0001
40-49	308	95	30.8	2.347 (1.694 – 3.254)	<.0001
50-59	203	79	38.9	3.353 (2.346 – 4.794)	<.0001
60-69	78	32	41.0	3.661 (2.217 – 6.047)	<.0001
>70	84	19	22.6	1.539 (.882 – 2.683)	.129
TOTAL	1780	460	25.8		

Table 28: Factors influencing the uptake of testing for hepatitis through the HepFree trial: male age

The impact of participant age on trial recruitment in males of non- Asian ethnicity. In this cohort, a significant association was identified between increasing age and attendance for viral hepatitis testing through the HepFree trial.

Age group	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
18-29	456	40	8.8	1 (ref)	
30-39	492	85	17.2	2.172 (1.456 - 3.24)	.0001
40-49	332	87	26.2	3.693 (2.46 – 5.54)	<.0001
50-59	213	63	29.6	4.368 (2.819 – 6.769)	<.0001
60-69	82	26	31.7	4.829 (2.739 – 8.514)	<.0001
>70	71	21	29.6	4.368 (2.387 – 7.992)	<.0001
TOTAL	1646	322	19.6		

Participation in testing was particularly low in males aged less than 39 in the non-Asian cohort, with only 13.2% of the eligible population consenting for testing. Of note, in the non-Asian cohort, testing was performed in less than 10% of the eligible population in males aged between 18-29. Participation in HepFree was significantly higher in all age groups compared to ages 18-29, p=<.0001.

Within the non-Asian cohort, further analysis of recruitment rates according to ethnicity was performed. Through exploring testing rates in each individual ethnic group, it may be possible to establish whether non-attendance was more frequently observed in particular ethnic groups, enabling the methodology of the trial to be reviewed and adapted to try and overcome this problem and increase subsequent engagement. Table 29 summarises the testing rates in each ethnic group contained within the non-Asian cohort.

Table 29: HepFree recruitment rates in ethnic groups within the non-Asian cohort

Rates of attendance for viral hepatitis testing in HepFree by individuals with a documented ethnicity other than Asian/British Asian in Bradford. Data expressed as a proportion of the total number of individuals registered at practices that were eligible to participate in the trial.

Ethnic category	No. of potential study participants	No. recruited	Percent of potential study population (%)
White	1457	411	28.2
Mixed	260	67	26.2
Black	655	139	21.2
Other	1055	166	15.7
TOTAL	3427	783	22.8

Abbreviations:

Mixed: Mixed/multiple ethnicities, **Black**: Black African/Caribbean/ British

Individuals with a Read code in their electronic medical record that did not give a clear indication of their ethnic origin engaged least frequently with testing through the trial. One such example of a Read code is 'other ethnic group'. In all other ethnic groups included in this sub-analysis, testing rates exceeded 20%. In order to try and gain additional information about the group of individuals with no meaningful code recorded to describe their ethnic origin, country of birth was explored. There was a Read code denoting country of birth in 470 of the 1,055 potential study participants with no documented ethnicity (44.5%). The countries of birth that were recorded in the electronic medical records of these individuals are summarised in Table 30.

Table 30: Country of origin of eligible individuals with no documented ethnicity on SystmOne

The country of origin of individuals identified as eligible for participation in HepFree in whom no meaningful ethnicity was documented on SystmOne.

Country of origin	No. of participants
Afghanistan	6
Albania	4
Argentina	1
Azerbaijan	1
Bahrain	1
Bangladesh	1
Brunei	3
Burkina Faso	1
Burma	1
Central African Republic	1
Czech Republic	37
Egypt	1
Estonia	2
Georgia	1
Ghana	1
Greece	3
India	2
Iran	7
Iraq	25
Italy	1
Kuwait	2
Latvia	20
Lebanon	2
Libya	6
Lithiuania	7
Malawi	1
Morocco	10
Nepal	4
Nigeria	3
Oman	1
Pakistan	36
Poland	74
Portugal	2
Romania	9
Russia	6
Saudi Arabia	5
Seychelles	1
Slovakia	159
Somalia	1
Spain	1
St Kitts and Nevis	1
Sudan	1
Syria	7
Thailand	1
Tunisia	2
Turkey	1
Ukraine	1
Venezuela	1
Vietnam	1
The former Yugoslavia	2
Zimbabwe	1
Yemen	1
TOTAL	470

More than 50% of the 470 individuals with a country of birth, but no ethnicity recorded, originated from countries within Eastern Europe. This raises the possibility that although these individuals were born in countries within Eastern Europe, their ethnicity originates from another part of the world, and they do not consider themselves as 'white European' ethnicity.

Once again, in the non-Asian cohort, recruitment and testing rates in English speakers were compared with non-English speakers.

Table 31: Factors influencing the uptake of testing for hepatitis through the HepFree trial: main spoken language

The impact of main spoken language; English versus non-English on trial recruitment in individuals of non-Asian ethnicity.

Language	No. of potential study participants	No. recruited	Percent of potential study population (%)	Univariate	
				OR (95% CI)	P
English	255	208	81.6	1 (ref)	
Other	2058	557	27.1	.084 (.060 - .117)	<.0001
Unknown	1114	18	1.6	.0037 (.00021 - .0065)	<.0001
TOTAL	3,427	783	22.8		

An analysis of testing rates by main spoken language in non-Asian participants produced the same results as were observed in the Asian cohort. Hepatitis testing was performed less frequently in individuals with a documented main spoken language other than English, 27.1% versus 81.6%. Again, English as a main spoken language had a statistically significant association with attendance for testing, OR 11.926, 95% CI: 8.564 – 16.61, p<.0001. The wide confidence interval is likely to be attributed to the sample sizes included in the analysis.

From analysis of participants recruited into HepFree based on ethnicity, similar themes in screening occurred in both the Asian and non-Asian cohorts. In HepFree, engagement rates were higher in females, in individuals of an advancing age and in those with English documented as a main spoken language.

5.2.4 Individuals declining the offer of screening

As summarised in Figure 15, 20,478 individuals were invited to attend for hepatitis testing in the ten HepFree practices included in this thesis. The uptake of testing in the invited population was 35.7%. Within the trial specific proforma published on S1, there was the option for a member of staff in the GP surgery to document occasions when potential study participants either contacted the practice on receipt of the invitation letter to formally decline the offer of participation in the trial and subsequent testing, occasions when potential study participants were offered the test face to face and declined, or occasions when potential study participants attended to consent for the trial but ultimately declined prior to testing been performed. If the section of the trial specific proforma labelled 'declined to participate in research' box was ticked, a Read code was recorded in the electronic medical record of that individual, and this data was available for collection by the trial team.

During the eighteen months that the trial was active within the practices, there were 1,065 episodes when the Read code 'declined to participate in research' was entered in an electronic record in a targeted testing practice. This figure represents 5.2% of the invited population.

5.3 Discussion

In this chapter, the methods used by practices to engage participants in HepFree were analysed. For the purpose of the analysis, an assumption was made that if consent and hepatitis testing occurred between days 1-31 of the invitation letter being sent, then recruitment was considered to be associated with the invitation letter. In the ten practices performing targeted testing, in 81.3% of cases, recruitment occurred either on day zero (the same day that the letter was generated) or after thirty-one days, in these participants, recruitment was therefore considered to be opportunistic. In the HepFree trial, opportunistic recruitment testing was proven to be more effective than letter invitation to attend for testing.

We do however recognise that it is rarely possible to apply such an arbitrary assumption to a real life situation. There are a multitude of factors that exist and that may influence an individual's decision to participate in testing that cannot be taken into account when simply measuring the number of days that have lapsed between an invitation letter being sent and an individual attending for testing. Cultural, social and economic factors, in addition to first-

hand experience of the consequences of hepatitis may all influence a person's decision making with respect to engaging in testing. As observed here, although in the majority of cases the letter may not have been the sole driving force prompting an individual to book an appointment for testing, the letter may have contributed to their decision to participate in some way. In view of this, we feel that the results of this analysis alone are not powerful enough to conclude that letter invitation is ineffective in future screening programmes directed at immigrants.

The results do however highlight the importance of modifying methods used to invite the target population in future targeted testing strategies, in order to optimise engagement by 'non-responders', The rigorous and efficient use of Read codes may help to facilitate this. It is arguable that generating an invitation letter is less onerous on members of staff compared to phone-calls, so as an initial method of invitation it is reasonable to continue to use this. Inputting a Read code at the time that an individual responds to the invitation would then allow the practice to be able to review 'non-responder' records and determine the next most appropriate method of invitation. The addition of an alert or prompt to the records of all 'non-responders' would act as a reminder to staff to discuss the testing/screening strategy if they have an episode of contact with them. If however, on reviewing the records of 'non-responders' it is clear that they rarely engage with primary care, a SMS or telephone call may be more effective. By coding each engagement method used and performing regular reviews of uptake rates in response to each method, an evaluation of the effectiveness of different interventions could be performed.

In Bradford, as a proportion of the population that were invited to participate in HepFree, higher rates of attendance were observed in females compared to males, 37.1% versus 29.1%. The majority of participants recruited for testing through HepFree were first generation immigrants, 72.8% versus 25.7%. It would have been both interesting and valuable to have been able to establish the uptake rate amongst all first and second generation immigrants that were eligible to participate from the ten practices. This was not possible however due to deficiencies in data available relating to country of origin for all potential study participants. From the data that was available for analysis, just over half of all cases (54%) had a documented country of birth; 43.6% were born outside of the UK and therefore first generation and 10.4% were second generation immigrants.

The increased attendance at hepatitis case finding initiatives by first generation immigrants observed is consistent with previous viral hepatitis studies conducted in migrant populations (301,303,304,331,332).

In order to investigate the impact of factors including gender, age and main spoken language on attendance for testing, depending on an individual's ethnicity, analysis was performed on two cohorts, Asian and non-Asian. Similar themes with regards to testing were identified in both of the cohorts analysed. Irrespective of ethnicity, it was evident that the HepFree trial failed to engage males to the same extent as females; in particular young males.

The pattern of recruitment observed in HepFree was not surprising. There are several possible explanations for the findings observed. In immigrant populations, unemployment rates are more prevalent in females, making it easier for this group to access appointments at the GP surgery during the day to engage with the HepFree trial. In addition to this, although not proven, as this group of individuals do not have work commitments, they may be more likely to socialise with other members of their community where they may be influenced by the views and opinions of their peers with regards to testing. Finally a report has demonstrated that ethnic minority females are more likely to report a limiting long-term illness compared to both white females and males of the same ethnicity and may therefore be more likely to attend appointments in primary care, increasing the number of available opportunities for trial recruitment to occur through opportunistic methods (333).

The pattern of recruitment observed in HepFree also reflects the demographics of the individuals that access primary care services in England. Apart from at extremes of age, females access medical services in primary care more frequently than males. In terms of the trial, this results in an increased number of opportunities for practice staff to engage with these potential study participants (334,335). In order to engage men more effectively in testing for hepatitis, one possibility may be to adapt the trial methodology and increase the number of locations used to perform testing, perhaps to include both places of worship, as well as places of work that employ large numbers of migrant workers in conjunction with testing in primary care.

In HepFree, recruitment and subsequent testing was observed less frequently in individuals that did not have English documented as a main spoken language. There are several possible explanations for why this finding might have occurred. Firstly, it may be related to the methods used by HepFree to invite potential study participants. Although the potential impact of a language barrier was addressed during the trial design and translations of both the invitation letter and patient information sheet produced, even with these modifications, letter invitation does not cater to individuals who are either illiterate in all languages, or those who speak and read a local dialect. In addition to difficulties in inviting potential participants due to language barriers, the consent form used at the time of recruitment into HepFree was written in English. This may have resulted in individuals that could not read English been reluctant to sign to participate in the trial.

Participation in HepFree by non-Asian participants was lower than in Asian participants. This finding may have occurred for multiple reasons discussed below. Firstly, it could be related to the ethnic composition of Bradford. Of the potential study participants invited to participate in the trial, 17,556 were Asian/British Asian ethnicity compared with 3,427 non-Asian. An alternative explanation is that this finding reflects awareness levels of viral hepatitis within the two cohorts. Due to the high prevalence of viral hepatitis in south Asian countries, in particular Pakistan, individuals of Asian ethnicity may be both more aware, or have more first-hand experience of the consequences of viral hepatitis. In addition to this first-hand experience, as previously discussed, several viral hepatitis awareness campaigns have previously been launched in Bradford, aimed in particular at south Asian communities. The finding of lower rates of engagement observed in the non-Asian cohort may be a reflection of this group of individuals' perceived risk of infection. Individuals of non-Asian ethnicity may either have a lower level of awareness about viral hepatitis and the consequences of long-term untreated infection, or alternatively may not be as concerned about their risk of infection compared to age-matched Asian individuals.

The differences in trial recruitment rates between the cohorts may also be a reflection of the overall health and health-needs of individuals within the non-Asian cohort. We established that engagement with the HepFree trial was predominantly the result of opportunistic recruitment methods; therefore, if non-Asian patients do not attend the practice as frequently for medical appointments, there would be fewer opportunities available to offer testing opportunistically to this cohort.

In 5.2% of cases, a Read code was entered into the electronic medical record of a potential study participant signifying that they had formally declined the offer to participate in the HepFree trial. This data does however have to be interpreted with caution. Firstly, the Read code used by the trial to record an individual's decision to not participate in the trial was not a 'HepFree specific' Read code. The Read code was a generic one, available in the catalogue of Read codes published and available for use on SystmOne. It is therefore possible that the Read code may have been used to document an individual's decision not to participate in another trial that was being conducted at the same time as HepFree. As well as potential inaccuracies with the Read code, the Read code data is not comprehensive as it fails to take into account individuals that received the letter but failed to respond. Failure to respond is highly suggestive that an individual has declined the offer of participation in the trial, therefore the number of potential study participants declining to participate in hepatitis testing could have been as high as 13,176.

In order to accurately establish the number of potential study participants that were invited and then subsequently declined the offer of hepatitis testing through HepFree, processes would have to be implemented to firstly ensure that all potential study participants received their invitation letter. A subsequent episode of contact would have to be made with each individual to confirm that those who had not booked an appointment for testing did not wish to participate. By doing this, an outcome for all participants that were invited would be recorded.

6. HepFree results: Prevalence of viral hepatitis in immigrant communities in Bradford.

6.1 Introduction

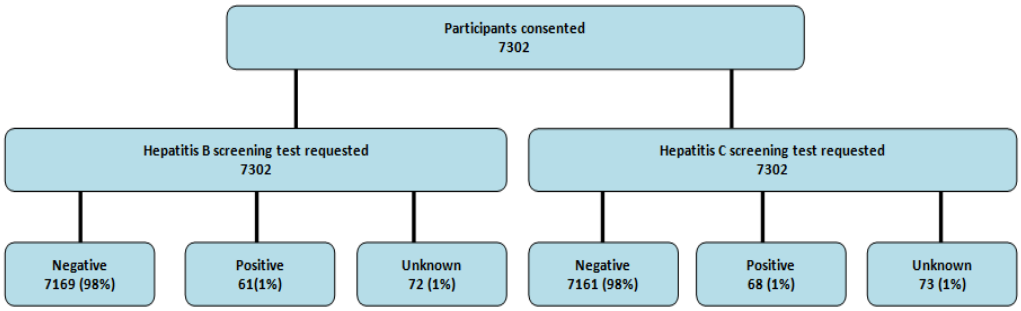
In this chapter I will present data on the prevalence of viral hepatitis in immigrant populations in Bradford acquired from the GP based case-finding trial HepFree. In particular I will describe the demographics and characteristics of study participants that tested positive for viral hepatitis. I will explore the prevalence of anti-HCV and HBsAg in different ethnic groups, genders and age groups, and aim to establish which groups are at highest risk of infection, and would therefore benefit most from implementation of a universal viral hepatitis screening programme.

For each participant that was tested as part of the HepFree trial, blood was taken and analysed to test for the both presence of HBsAg and anti-HCV. As discussed previously, the presence of HBsAg in serum indicates chronic infection with HBV. Anti-HCV, if present, indicates that an individual had been exposed to HCV, and requires further investigation with an RNA test to determine whether there is evidence of chronic infection.

6.2 Results

HepFree recruited 7,302 participants in Bradford and 14, 604 results were reported. From all viral hepatitis tests performed, 145 results were not available; this accounts for 1% of all tests performed (Figure 26). In 72 cases the laboratory failed to report both the HBsAg and anti-HCV result for subjects tested, and in one further case, the HBsAg result was available but the anti–HCV result had not been reported. Results were not generated by the laboratory for the following reasons; inadequate sample volume sent for analysis, sample haemolysis, incorrect labelling of the sample sent for analysis, and discrepancies in participant information between the sample bottle and sample request form.

Figure 26: The results of targeted testing for viral hepatitis in the HepFree trial in Bradford



A flow chart summarising the results of viral hepatitis tests requested in the HepFree trial population included in this analysis. 7,302 individuals were consented and underwent testing. There were 61 cases of chronic HBV and 68 cases with a positive test for anti-HCV.

The prevalence of viral hepatitis, defined as either the presence of anti-HCV or HBsAg in the tested population was 1.77%; anti-HCV 0.9% and HBsAg 0.8% respectively. In first generation immigrants undergoing testing, the prevalence of anti-HCV was 1.2%, and HBsAg was 1.1%. In second generation, the results were 0.32% and 0.27% respectively. First generation immigrants had 3.72 times the risk of having viral hepatitis compared to second generation immigrants, 95% CI 2.010 – 6.887. Expressed as a percent relative effect, first generation immigrants had 272% increase in risk of being infected with viral hepatitis compared to second generation immigrants.

All participants with a positive viral hepatitis test were referred for review in a secondary care outpatient clinic. Subjects with a positive anti-HCV test had a subsequent HCV RNA test performed automatically by the laboratory to establish chronic infection status. During the diagnostic assessment in secondary care it became apparent that 18 individuals with a positive test for anti-HCV had previously received antiviral therapy for chronic HCV. Within this previously treated cohort, there was no recurrence of disease. In individuals with no prior history of treatment with antiviral therapy, RNA positive chronic hepatitis C was identified in 25 cases (50%) and spontaneous virus eradication had occurred in the remaining 25 cases (50%).

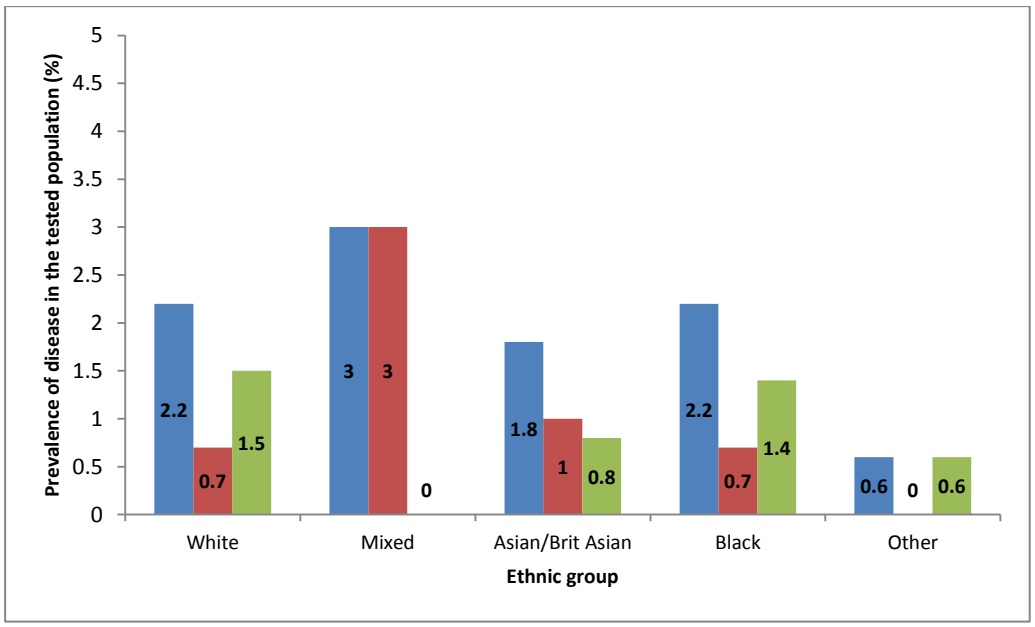
6.2.1 The demography of individuals with a positive viral hepatitis test

Figures 27 to 29 summarise the demography of participants with a positive test for hepatitis. In all figures, the coloured bars represent the following values:

- Test positive for viral hepatitis
- Test positive for Anti-HCV
- Test positive for HBsAg

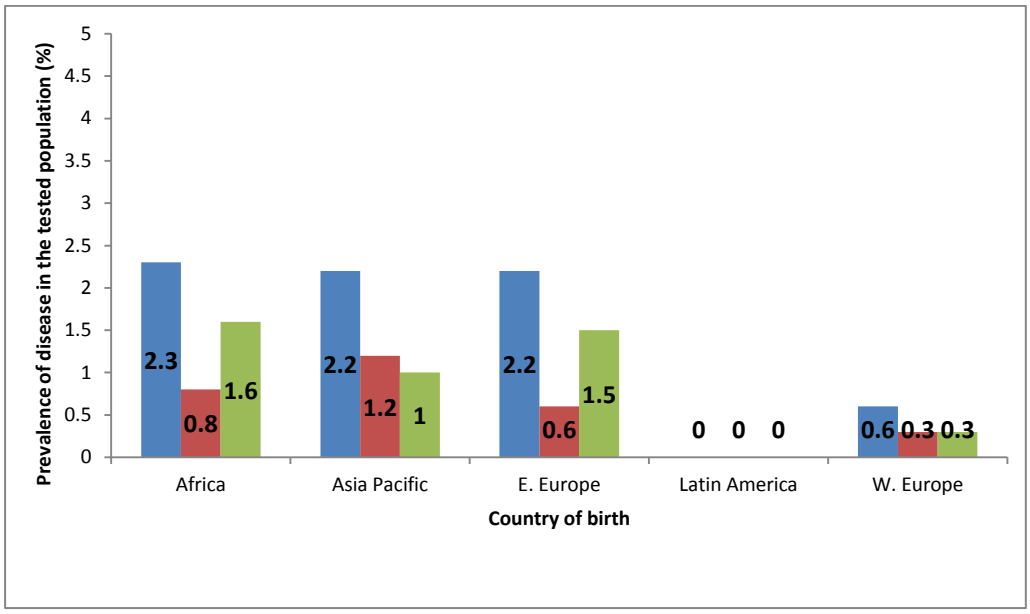
Figure 27: The prevalence of viral hepatitis in individuals according to ethnicity

Note the change in the axis scale.



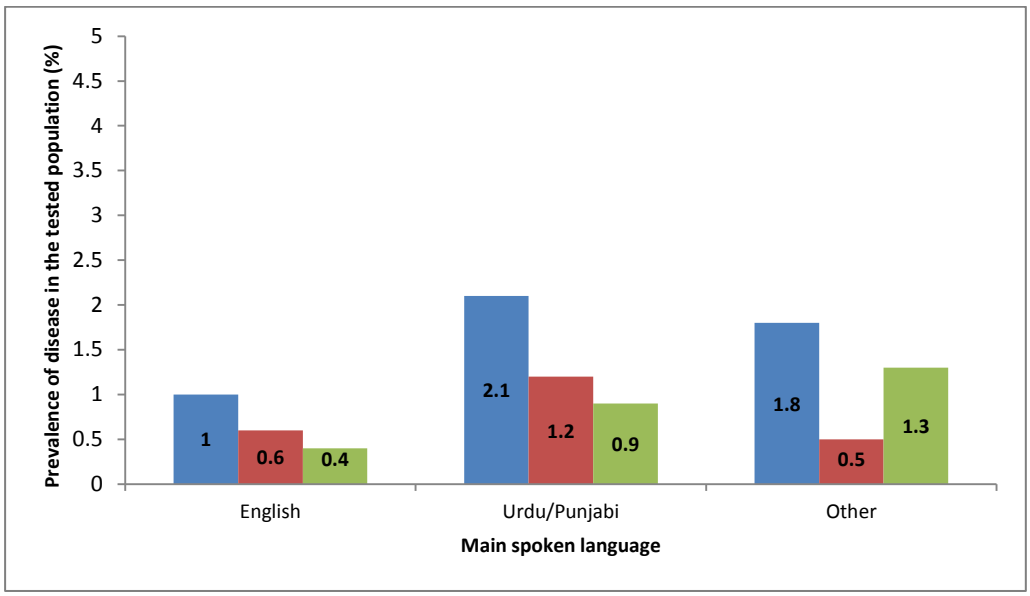
A column chart summarising the prevalence of disease according to documented ethnicity. The highest prevalence of viral hepatitis was identified in individuals with 'mixed' ethnicity however this is likely to be a consequence of the sample size.

Figure 28: The prevalence of viral hepatitis in individuals according to country of birth



A column chart summarising the prevalence of disease according to documented country of birth. The lowest prevalence was identified in individuals originating from countries within Western Europe; this is likely to reflect the second generation population tested as part of the trial.

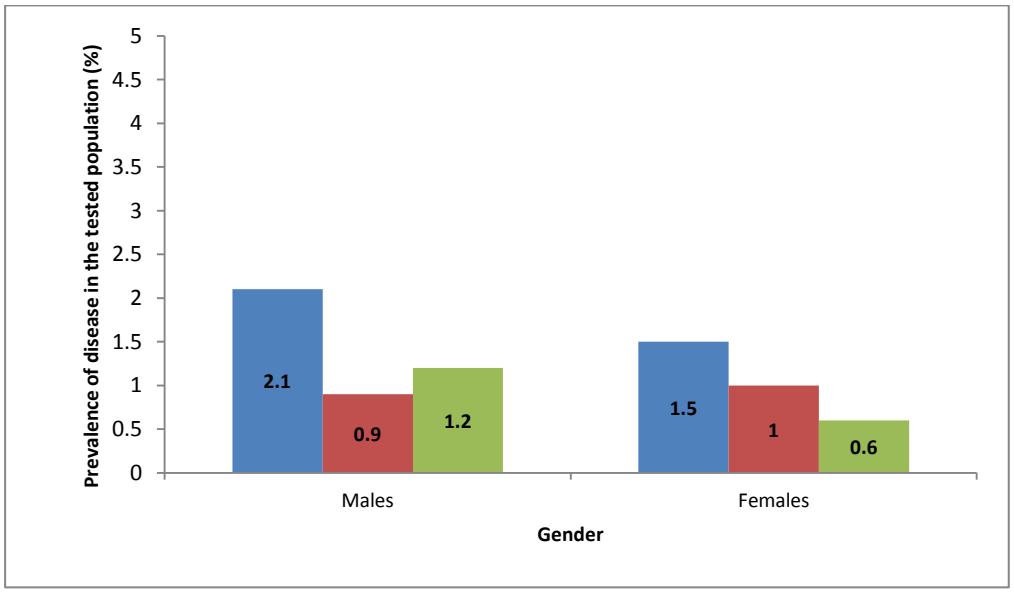
Figure 29: The prevalence of viral hepatitis in individuals according to main spoken language



A column chart summarising the prevalence of viral hepatitis according to documented main spoken language. The highest prevalence of viral hepatitis was identified in individuals with a main spoken language of Urdu/Punjabi and was lowest in individuals with a documented main spoken language of English.

Positive screening tests were most frequently observed in individuals with a documented main spoken language of Urdu/Punjabi (Figure 29). This is an important finding as the results of the analysis performed on factors that influence uptake of testing demonstrated that non-English speakers were less likely to engage with the trial compared to English speakers, therefore we could be under-diagnosing viral hepatitis in this group of migrants.

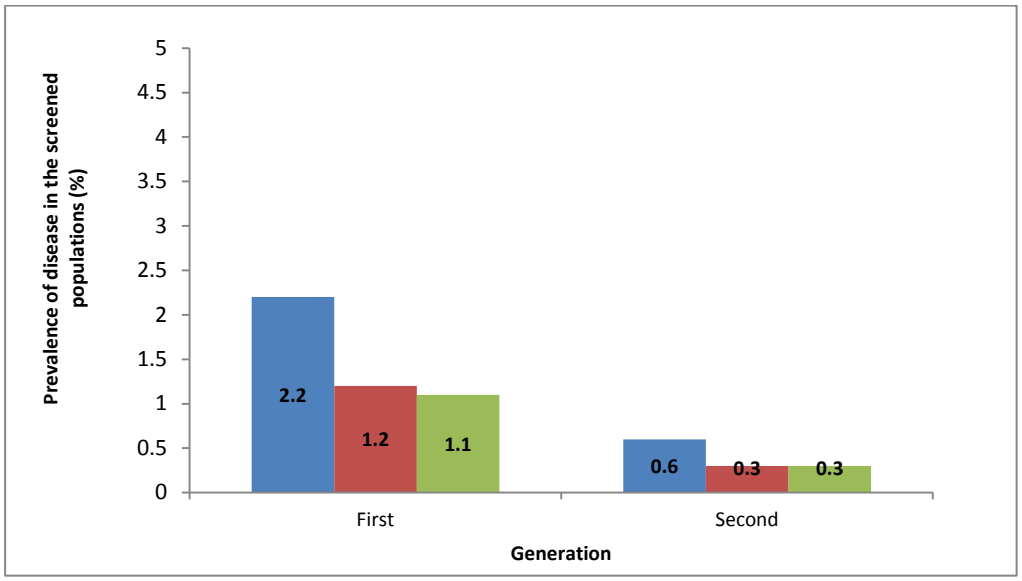
Figure 30: The prevalence of viral hepatitis in individuals according to gender



A column chart summarising the prevalence of viral hepatitis in the trial cohort according to gender. The highest prevalence was identified in males that attended for testing; 2.1% versus 1.5%.

The overall prevalence of viral hepatitis was higher in males recruited to the trial compared to females, despite more females engaging with testing through HepFree. Interestingly the prevalence of HBV in males was 1.2% compared to only 0.6% in females. This finding is discussed in more detail below. The prevalence according to gender highlights the importance of adapting the methodology of a future screening programme to encourage participation by male immigrants.

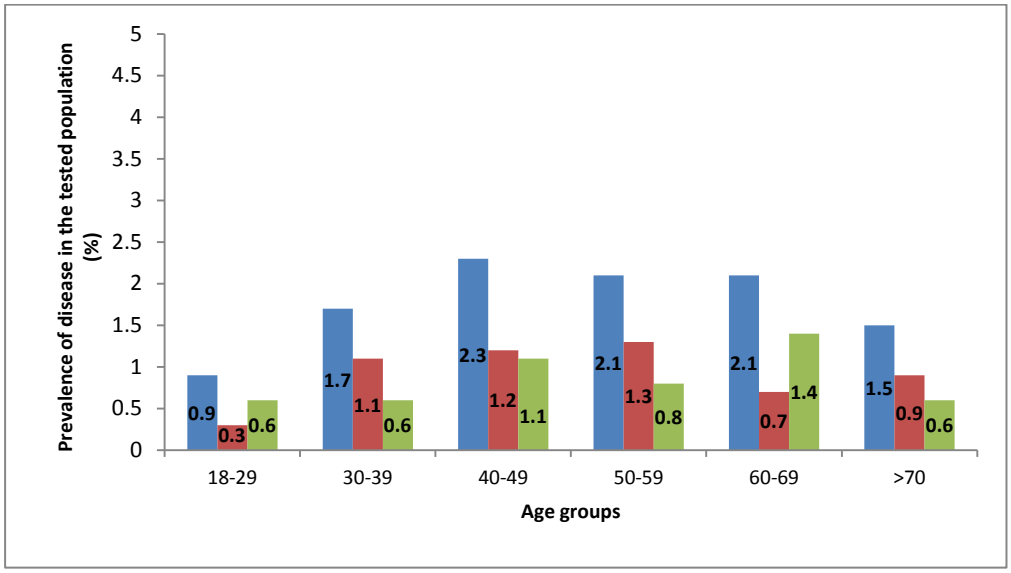
Figure 31: The prevalence of viral hepatitis in individuals according to generation; first versus second.



A column chart summarising the prevalence of disease in the HepFree population according to generation. The highest prevalence of disease was identified in individuals born outside of the UK, also known as first generation; 2.2% versus 0.6%.

Consistent with results from previous screening studies, viral hepatitis was identified more frequently in first generation immigrants, compared to second generation immigrants.

Figure 32: The prevalence of viral hepatitis in individuals according to age (Grouped Data)



A column chart summarising the prevalence of disease in the HepFree population according to age (grouped data). The prevalence of disease increased with advancing age (>40 years).

Finally, when exploring the prevalence of disease in different age groups, there was a higher prevalence of disease identified in individuals of advancing age. This is consistent with the finding that more cases of infection were identified in first generation immigrants. In HepFree, first generation immigrants engaging with the trial were older than second generation immigrants (Figure 32).

A more in depth analysis was performed on the cohorts of participants with viral hepatitis in order to gain a better understanding about the demographics of individuals that should be targeted by future screening programmes because of an increased risk of viral infection. Data obtained was analysed by ethnicity, age group and gender. Cases of HBV and HCV infection were analysed individually.

The following trial participants were excluded from this analysis:

1. Individuals with no viral hepatitis result reported.
2. Individuals that participated in the trial with an unrecorded gender.
3. Individuals that participated in the trial with an unrecorded ethnicity.

6.2.2 The demographics of the Hepatitis C positive cohort

6.2.2.1 Ethnicity

An equal proportion of positive anti-HCV tests were observed in individuals of White, Asian/British Asian and Black African/Caribbean/British ethnicities (Table 32). A higher prevalence of anti-HCV positive tests were identified in individuals that attended for testing with a Read code denoting 'mixed/multiple' ethnicity in their electronic medical record. There were no positive anti-HCV tests in the cohort of individuals with an absent field for ethnicity. In both the 'mixed/multiple' ethnic category and the cohort of individuals with no ethnic code documented, the numbers of individuals participating in testing were very low and therefore the results obtained are likely to be outliers, reflecting the small sample size.

Table 32: The prevalence of anti-HCV in trial participants according to ethnicity

The prevalence of anti-HCV in the tested population in each ethnic group of interest.

Ethnic group	Number eligible	Number tested	Number positive	Percent of total tested	Percent of total eligible	Univariate	
						OR (95% CI)	P
White	1457	399	3	0.8	0.2	1 (ref)	
Mixed/Multiple	260	66	2	3.0	0.8	4.135 (.678 – 25.233)	.124
Asian/Brit Asian	17552	6451	62	1.0	0.4	1.284 (.401 – 4.109)	.422
Black	654	135	1	0.7	0.2	.988 (.102 – 9.575)	.991
Other ethnicity	1055	161	0	0	0	.352 (.0181 – 6.846)	.490
Total	20,978	7,212	68	0.9	0.3		

6.2.2.2 Age

Testing for the presence of anti-HCV appeared to be particularly beneficial in individuals aged between 40 and 59; the prevalence of a positive test in this cohort was 1.2%. The role of future screening strategies in young adults aged 18-29 is dubious given the very low prevalence observed.

The low rate of infection identified in this age group is likely to be related to the country of birth of participants included within it. As discussed previously, in the trial, second generation immigrants were younger than first generation so it is likely that testing in this age group was primarily focussed on second generation immigrants (Table 33).

Table 33: The prevalence of anti-HCV in trial participants according to age (grouped data)

The prevalence of anti-HCV in the tested population organised by age group. A very low prevalence was identified in individuals aged 18-29, likely a reflection of their country of origin (first versus second).

Age group	Number eligible	Number screened	Number positive	Percent of total tested	Percent of total eligible	Univariate	
						OR (95% CI)	P
18-29	6862	1414	4	0.3	0.1	1 (ref)	
30-39	6200	1917	21	1.1	0.3	3.904 (1.337 – 11.399)	.012
40-49	4122	1677	20	1.2	0.5	4.255 (1.451 – 12.477)	.008
50-59	2130	980	13	1.3	0.6	4.739 (1.541 – 14.577)	.007
60-69	1439	700	5	0.7	0.3	2.536 (.679 – 9.473)	.166
>70	1229	524	5	1.0	0.4	3.396 (.908 – 12.695)	.007
Total	21,982	7,212	68	0.9	0.3		

6.2.2.3 Gender

Table 34: The prevalence of anti-HCV in trial participants according to gender

The prevalence of anti-HCV was similar in both females and males 0.4% versus 0.3% of the total eligible population and 1.0% versus 0.9% of the total population recruited and tested through HepFree.

Gender	Number eligible	Number screened	Number positive	Percent of total tested	Percent of total eligible	Univariate	
						OR (95%CI)	P
Female	11,256	4128	40	1.0	0.4	1 (ref)	
Male	10,719	3084	28	0.9	0.3	.936 (.576 – 1.521)	.791
Total	21,975	7,212	68	0.9	0.3		

There was no statistically significant difference identified between the prevalence of infection in females and males included in the sample, p = .791.

6.2.2.4 Binomial logistic regression

A binomial logistic regression was performed to understand whether a positive HCV test could be predicted based on an individual's age, country of birth and gender. For the purpose of this analysis due to the small sample size, country of birth was categorised as either 'Asia Pacific' or 'Other'. Table 35 demonstrates the odds ratios and significance of the predictor variables. Of the variables entered into the model, only country of origin was statistically significant. Individuals originating from Asia-Pacific were 3.129 times more likely to be anti-HCV positive, 95% C.I 1.554-6.301. For both gender, and the continuous variable age, 95% confidence intervals contained 1.0; therefore the association was not significant at the .05 significance level.

Table 35: Binomial logistic regression HCV

A binomial logistic regression using data collected from individuals with a positive anti-HCV test.

Independent variable	**B**	**S.E**	**Sig**	**Exp(B)**	**95% CI for EXP (B)**	
					Lower	**Upper**
Age	-.001	.008	.922	.999	.983	1.015
Gender	-.075	.249	.762	.927	.570	1.510
Country	**1.141**	**.357**	**.001**	**3.129**	**1.554**	**6.301**
Constant	-5.426	.433	.000	.004		

6.2.3 The demographics of the hepatitis B positive cohort

6.2.3.1 Ethnicity

The highest prevalence of chronic hepatitis B was identified in Black African/Caribbean/British participants that attended for testing; 2.2%. Similar to the results of the HCV screening test, no cases of infection were identified in subjects with no meaningful ethnicity documented.

Table 36: The prevalence of HBsAg in trial participants according to ethnicity

The prevalence of anti-HCV in the tested population in each ethnic group of interest. The highest prevalence of HBV was identified in Black African/Caribbean/British participants attending for testing.

Ethnic group	Number eligible	Number screened	Number positive	Percent of total tested	Percent of total eligible	Univariate	
						OR (95% CI)	P
White	1457	399	6	1.5	0.4	1 (ref)	
Mixed/Multiple	260	66	0	0	0	0.455 (.0253-8.176)	.593
Asian/Brit Asian	17552	6451	52	0.8	0.3	.532 (.227-1.247)	.147
Black	654	135	3	2.2	0.5	1.489 (.367 – 6.036)	.578
Other ethnicity	1055	161	0	0	0	.187 (.011 – 3.347)	.255
Total	20,978	7,212	61	0.8	0.3		

6.2.3.2 Age

As in the anti-HCV cohort, the prevalence of HBsAg in young adults aged 18-29 who attended for testing was very low; 0.6%. There was a statistically significant increase in the prevalence of HBsAg in participants aged 60-69 compared to the baseline group for comparison which was 18-29.

Table 37: The prevalence of HBsAg in trial participants according to age (grouped data)

The prevalence of HBsAg in the tested population organised by age group. A very low prevalence was identified in individuals aged 18-29, likely a reflection of their country of origin (first versus second).

Age group	Number eligible	Number screened	Number positive	Percent of total tested	Percent of total eligible	Univariate	
						OR (95% CI)	P
18-29	6862	1414	9	0.6	0.1	1 (ref)	
30-39	6200	1917	12	0.6	0.2	0.983 (.413–2.340)	.97
40-49	4122	1677	19	1.1	0.5	1.789 (.807 – 3.967)	.152
50-59	2130	980	8	0.8	0.4	1.285 (0.494 – 3.342)	.0607
60-69	1439	700	10	1.4	0.7	2.262 (.915 – 5.594)	.008
>70	1229	524	3	0.6	0.2	.899 (.242 – 3.33)	.873
Total	21,982	7,212	61	0.8	0.3		

6.2.3.3 Gender

There was a statistically significant increase in the prevalence of HBV in the male population that attended for screening compared to the female population, OR 2.229, p=.003. This finding may be a consequence of other screening initiatives which exist for females in the UK (Table 38).

Table 38: The prevalence of HBsAg in trial participants according to gender

The prevalence of a positive test for HBsAg was significantly higher in males tested through HepFree compared to females, p = <.003.

Gender	Number eligible	Number screened	Number positive	Percent of total tested	Percent of total eligible	Univariate	
						OR (95%CI)	P
Female	11,256	4128	23	0.6	0.2	1 (ref)	
Male	10,719	3084	38	1.2	0.4	2.227 (1.324 – 3.745)	.003
Total	21,975	7,212	61	0.8	0.3		

6.2.3.4 Binomial logistic regression

A binomial logistic regression was performed to understand whether a positive HBV test could be predicted based on participant age, country of birth and gender. For the purpose of this analysis due to the small sample size, country of birth was categorised as either Asia Pacific or other. Table 39 demonstrates the odds ratios and significance of the predictor variables. Of the variables entered into the model, only male gender was statistically significant. In this population, males were 2.209 times more likely to be HBsAg positive, 95% C.I (1.311-3.721) as shown in Table 39. For both country of origin and the continuous variable age, 95% confidence intervals contain 1.0, therefore the association is not significant at the .05 significance level.

Table 39: Binomial logistic regression in HBsAg

A binomial logistic regression using data collected from individuals with a positive HBsAg test.

Independent variable	**B**	**S.E**	**Sig**	**Exp(B)**	**95% CI for EXP (B)**	
					Lower	**Upper**
Age	.004	.009	.666	1.004	.987	1.021
Gender	**.792**	**.266**	**.003**	**2.209**	**1.311**	**3.721**
Country	.508	.325	.118	1.661	.879	3.140
Constant	-5.678	.434	.000	.003		

6.2.4 Staging of disease in HepFree participants

All participants with chronic viral hepatitis diagnosed through HepFree were invited to attend a diagnostic assessment with subsequent appointments for investigations in secondary care in order to stage the severity of their disease and to help guide management. For participants with chronic HCV, staging was primarily performed using either transient elastography (Fibroscan®), a percutaneous ultrasound guided liver biopsy, or a combination of the two. For participants with chronic HBV, in addition to Fibroscan® and USS guided liver biopsy, disease activity was established by serum liver function testing and HBV VL analysis. In HBV, active disease is defined as a HBV VL of more than 2000IU/mL in combination with an elevated ALT.

In the trial, one hundred percent of participants with chronic HCV attended both the diagnostic and disease staging assessment visits. In the cohort of participants diagnosed with chronic HBV, 16 individuals (26%) were already known to secondary care and engaged with follow up and a further 7% did not engage with follow-up through the trial. Results will therefore be presented for forty-one participants with a new diagnosis of chronic HBV that engaged with HepFree follow-up.

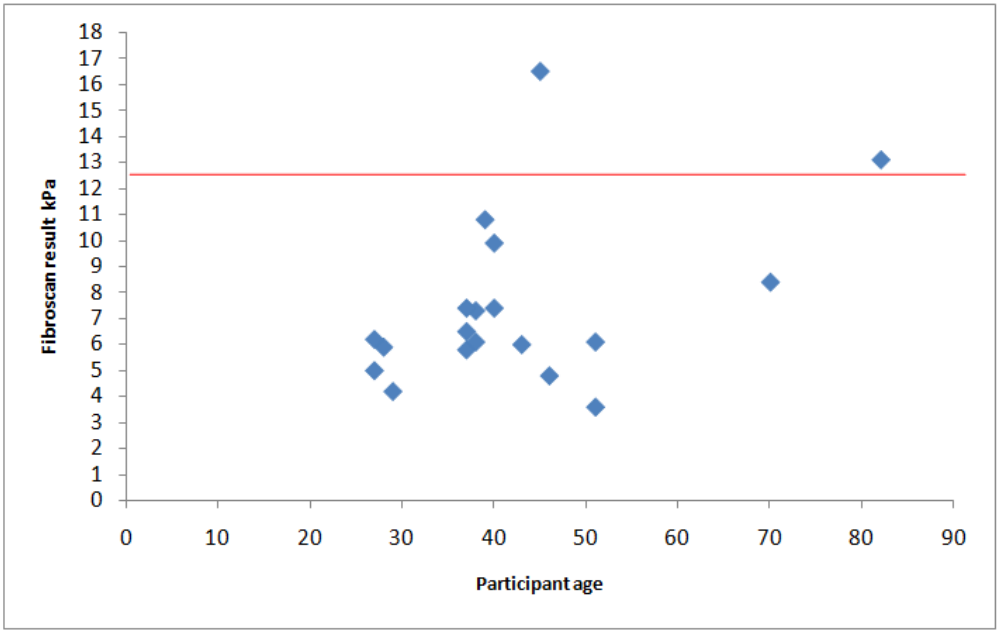
Table 40: Baseline characteristics of participants with chronic HCV diagnosed through HepFree

The baseline characteristics and fibrosis assessment outcomes for trial participants diagnosed with RNA positive chronic HCV.

Gender (M/F)	Age	Country of origin	HCV genotype	Fibroscan® kPa (Metavir stage)	Ishak fibrosis stage
F	27	Pakistan	3	5.0 (0-1)	
F	29	Pakistan	3	4.2 (0-1)	1
M	59	Czech Republic	1	48 (4)	
F	41	Pakistan	3		2
F	70	Pakistan	3	8.4 (1-2)	
F	45	Pakistan	3	16.5 (4)	3
F	51	Pakistan	1	3.6 (0-1)	
M	27	Pakistan	3		5
M	46	Pakistan	3	4.8 (0-1)	1
F	28	Pakistan	3	5.9 (0-1)	
M	35	Pakistan	3		2
F	51	Pakistan	3	6.1 (0-1)	2
F	82	Pakistan	3	13.1 (3-4)	
M	73	Pakistan	3		2
M	39	Pakistan	3	10.8 (3)	
F	40	Pakistan	3	7.4 (1-2)	
F	37	Pakistan	3	6.5 (1)	
M	43	Pakistan	3	6.0 (0-1)	1
F	37	Pakistan	3	5.8 (0-1)	1
M	40	Pakistan	3	9.9 (3)	6
F	38	Pakistan	3	6.1 (0-1)	
M	31	UK	1		2-3
M	38	Pakistan	3	7.3 (1-2)	1-2
M	37	Pakistan	3	7.4 (1-2)	2
M	27	Pakistan	3	6.2 (0-1)	1

In 20% (5/25) of cases diagnosed with chronic HCV through the HepFree trial there was evidence of advanced fibrosis on either transient elastography or percutaneous liver biopsy (eKPa 12.5, Metavir stage 4, Ishak stage 5/6).

Figure 33: Transient elastography assessment in HepFree participants with chronic HCV



A scatter plot of participant age (x-axis) and transient elastography liver stiffness score (kPa) (y-axis) in HepFree participants with chronic HCV that underwent fibrosis assessment using Fibroscan®. The horizontal red line at 12.5kPa denotes cirrhosis. In this scatter plot, no correlation was identified between participant age and severity of disease; Pearson correlation coefficient, r = 0.3841, n = 20, p = 0.0095. Data from the one outlier kPa 48.0 was excluded from this figure.

In the HepFree cohort of participants with chronic HCV no correlation was identified between participant age and severity of disease using transient elastography liver stiffness score.

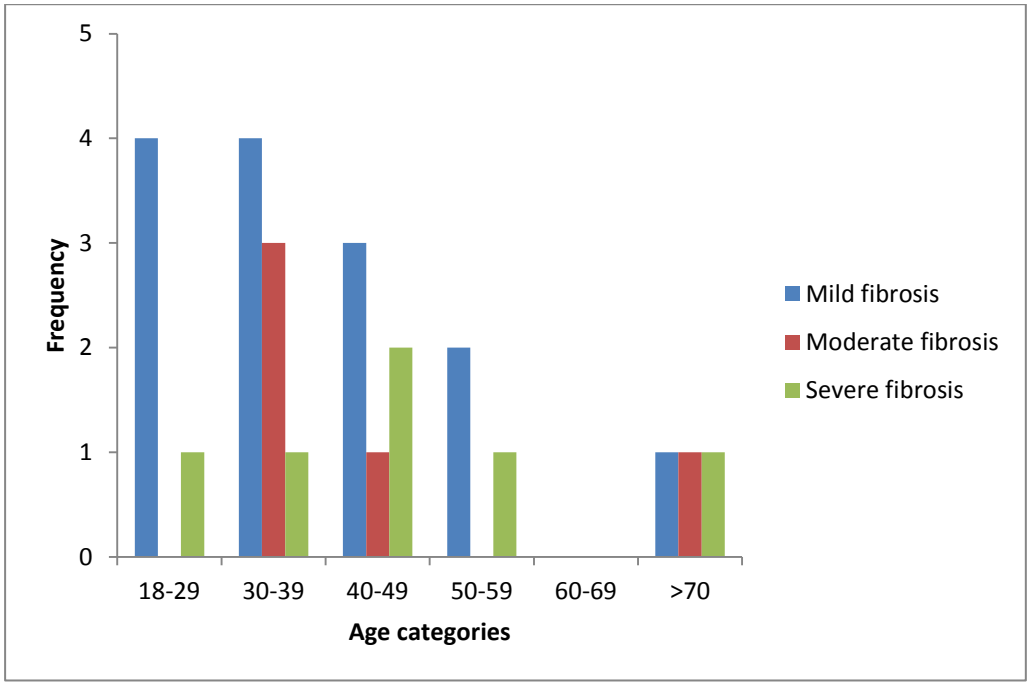
The severity of liver disease in different age groups of individuals with chronic HCV is displayed in Figure 34. Liver disease severity was classified as mild, moderate and severe using the following criteria:

Severity of liver disease	Metavir fibrosis score
Mild	0-1
Moderate	2
Severe	≥ 3

Due to the small number of individuals identified through HepFree screening it is difficult to draw conclusions pertaining to the severity of disease and duration of infection. In this cohort, mild disease was more frequently observed in individuals aged 18-30, individuals in

this age group also had evidence of severe fibrosis suggesting that long-term infection with the virus for more than twenty years is a risk factor for the development of cirrhosis.

Figure 34: The severity of liver disease in individuals diagnosed with chronic HCV



A column chart comparing participant age (grouped data, x-axis) and severity of liver disease, according to Metavir fibrosis score (frequency of diagnosis, y-axis) in individuals with RNA positive chronic HCV diagnosed through HepFree. Mild disease was more frequently observed in individuals aged 18-30, however there were cases of severe fibrosis in this age group suggesting that long-term infection with the virus for more than twenty years is a risk factor for the development of cirrhosis.

Table 41: Baseline characteristics of participants with chronic HBV diagnosed through HepFree

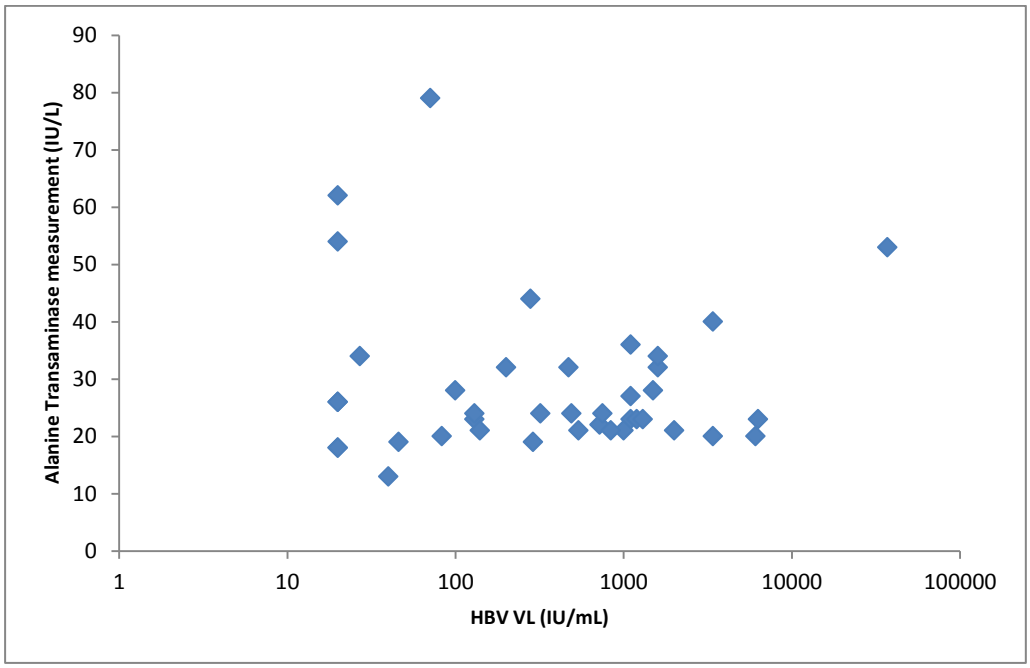
The baseline characteristics and fibrosis assessment outcomes for trial participants newly diagnosed with chronic HBV who attended for diagnostic assessment in secondary care.

Gender (M/F)	Age (yrs)	Country of Birth	HBV genotype	eAg status	HBV VL (IU/mL)	ALT (IU/L)	Fibroscan® kPa (Metavir stage)	Treatment indicated
M	46	Pakistan	D1	Neg	1.1×10^3	27	4.1 (0-1)	
M	22	UK	D1	Pos	1.7×10^8	92	4.6 (0-1)	Y
M	36	Pakistan		Neg	1.3×10^2	23	4.9 (0-1)	
F	53	Lithiuania	D1	Neg	3.2×10^2	24	5.9 (0-1)	
M	34	Bangladesh	D2	Neg	2.8×10^2	44	5.8 (0-1)	
M	35	Gambia	A1	Neg	4.7×10^2	32	8.7 (2)	
M	55	Pakistan		Neg	<20	62	11.4 (3)	
M	21	Pakistan	D1	Neg	1.6×10^3	32	5.6 (0-1)	
F	62	Pakistan		Neg	<20	26	8.2 (2)	
F	48	Pakistan	D1	Neg	6.3×10^2	23	5.0 (0-1)	
M	48	Pakistan		Neg	$10. \times 10^2$	28	4.0 (0-1)	
M	58	Pakistan	D1	Neg	3.4×10^3	40	6.8 (0-1)	
F	27	Pakistan	D1	Neg	3.4×10^3	20	5.6 (0-1)	
M	63	Pakistan		Neg	1.3×10^2	24	6.8 (0-1)	
M	47	Bangladesh	D2	Neg	1.1×10^3	23	5.4 (0-1)	
F	61	Pakistan		Neg	46	19	4.1 (0-1)	
M	60	Pakistan	D1	Neg	2.0×10^2	32	2.0 (0-1)	
F	67	Pakistan	D1	Neg	1.2×10^3	23	8.9 (2-3)	
F	52	India		Neg	<20	18	4.9 (0-1)	
F	56	Pakistan	D1	Neg	1.0×10^3	21	4.1 (0-1)	
M	62	Pakistan		Neg	7.2×10^2	22	4.5 (0-1)	
M	41	Pakistan	D1	Neg	2.0×10^3	21	3.3 (0-1)	
M	40	Pakistan		Neg	1.4×10^2	21	7.8 (1-2)	
M	39	Pakistan		Neg	71	79	9.4 (2-3)	
M	48	Pakistan	D1	Neg	7.5×10^2	24	3.2 (0-1)	
M	28	Pakistan		Neg	<20	54	4.0 (0-1)	
M	38	Pakistan		Neg	83	20	5.3 (0-1)	
M	42	Pakistan	D1	Neg	1.5×10^3	28	5.8 (1)	
M	42	Pakistan		Neg	27	34	12.6 (3)	Y
F	59	India	D1	Neg	1.3×10^3	23	4.2 (0-1)	
M	57	Pakistan		Neg	5.4×10^2	21	6.4 (0-1)	
M	22	UK		Neg	4.9×10^2	24	4.7 (0-1)	
M	25	UK		Neg	20	26	4.8 (0-1)	
F	45	Pakistan		Neg	2.9×10^2	19	5.3 (0-1)	
F	44	Pakistan		Neg	<20	18	3.3 (0-1)	
M	39	Ghana	E	Neg	1.6×10^3	34	4.7 (0-1)	
F	32	Pakistan	D1	Neg	6.1×10^3	20	4.8 (0-1)	
M	83	Bangladesh		Neg	<40	13	6.1 (0-1)	
M	33	Bangladesh	D1	Neg	1.1×10^3	36	7.8 (2)	
M	48	Poland	A2	Neg	3.7×10^4	53	10.1 (2-3)	Y
M	42	Pakistan	D1	Neg	8.4×10^2	21	5.4 (0-1)	

In the cohort of newly diagnosed individuals with chronic HBV that attended for assessment, 98% (40/41) had undergone seroconversion and were anti-HBe positive. A genotype was available in 54% of cases (22/41). In individuals with sufficient viral load to enable genotyping, the most prevalent genotype in this was D (46.3%). This result was unsurprising given the high number of participants originating from countries in the group Asia Pacific.

In 15% of cases (6/41) the VL was elevated over 2000IU/mL. Of those participants with an elevated VL, 33% (2/6) also had an elevated ALT above the upper limit of normal (reference range 40IU/L) suggesting active disease requiring regular monitoring in addition to interpretation of the fibrosis score obtained from transient elastography or from USS guided liver biopsy to establish whether antiviral therapy would be required.

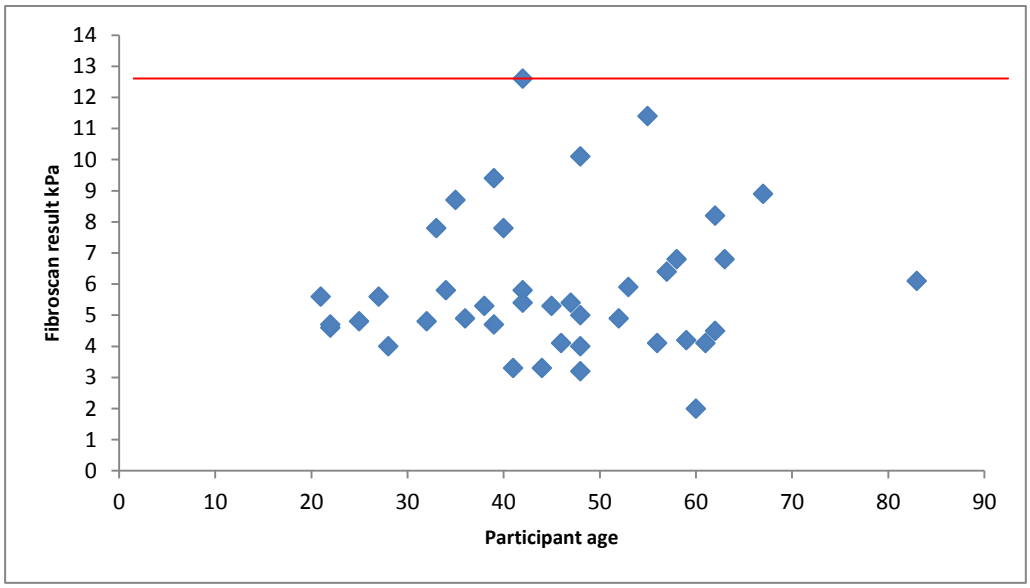
Figure 35: Hepatitis B viral load and serum ALT measurement in individuals with chronic HBV



A **s**catter plot of HBV viral load and serum ALT measurement in individuals with chronic HBV who attended for assessment. No correlation was identified between HBV viral load and serum ALT, Pearson correlation coefficient, r = 0.2521, n = 40, p = 0.117.

No correlation was identified between HBV viral load and ALT measurement in individuals with chronic HBV in the HepFree cohort. This demonstrates that serum ALT alone cannot be reliably used as a marker of activity in HBV.

Figure 36: Transient elastography assessment in HepFree participants with chronic HBV



A scatter plot of participant age (x-axis) and transient elastography liver stiffness score (kPa) (y-axis) in HepFree participants with chronic HBV that underwent fibrosis assessment using Fibroscan®. The horizontal red line at 12.5 kPa denotes cirrhosis. In this scatter plot, no correlation was identified between participant age and severity of disease using transient elastography liver stiffness score; Pearson correlation coefficient, r = 0.0857, n = 41, p = .5942.

In this cohort of individuals with chronic HBV no correlation was identified between participant age and severity of disease using transient elastography liver stiffness score.

According to EASL guidelines (32), treatment is indicated in individuals with chronic HBV that fulfil the following criteria:

HBeAg positive HBV	Anti-HBe positive HBV	HBV associated cirrhosis
HBV DNA >2.0 x10^3IU/mL and/or ALT >ULN with histological evidence of moderate to severe disease on liver biopsy	HBV DNA>2.0 x10^3IU/mL and/or ALT>ULN with histological evidence of moderate to severe disease on liver biopsy	<u>Compensated</u> Any detectable level of HBV DNA. <u>Decompensated</u> Any detectable level of HBV DNA.

Treatment was indicated in 5% of individuals that were diagnosed with chronic HBV in Bradford. The relatively small number requiring treatment may be related to the ethnic profile of individuals attending for testing. In Bradford, testing was predominantly performed in individuals of Pakistani origin, and D was the prevalent genotype identified in this group. Adverse clinical outcomes including the development of cirrhosis and/or HCC are more frequently associated with genotypes B and C, therefore the number of individuals tested through HepFree that require treatment may be higher in areas of the UK conducting the study where there are higher numbers of migrants residing that originate from other countries within Asia and Africa.

6.3 Discussion

In medicine, screening is a strategy employed within a population to identify the presence of an undiagnosed disease in individuals without signs or symptoms. The aim of targeted testing in viral hepatitis is to identify individuals early, prior to the onset of complications that arise as a result of long-term infection enabling interventions to be performed that reduce morbidity and mortality associated with the disease. HepFree trial results in Bradford have suggested that the prevalence of viral hepatitis is higher in immigrants residing in the UK compared to the indigenous population. Analysis of the HepFree dataset identified a prevalence of viral hepatitis of 2.2%, with disease more commonly identified in individuals with a main spoken language other than English. This result is particularly important for several reasons. Firstly, it is well documented that language barriers can result in inadequate access to appropriate healthcare services by users. In terms of the trial methodology, the use of letter invitations may have resulted in exclusion of individuals unable to speak and read English.

The prevalence of viral hepatitis in immigrants attending for screening who were born in England (second generation) was low, with rates of detection comparable with the rates of infection in the non-immigrant population. There is an argument therefore that future screening efforts that concentrate solely on first generation immigrants would be more beneficial. Adapting the methodology of future screening trials to reflect this however may result in missed cases of infection. It is feasible that children born to first generation migrants will spend prolonged periods of time overseas in countries where the risk of infection is much

greater, either visiting or caring for relatives and this group would therefore still be at an increased risk of acquiring the infection.

Our results demonstrated that individuals that attended for testing through HepFree engaged with subsequent follow up. One hundred percent of individuals with a positive anti-HCV test attended secondary care for diagnostic assessment. Although the numbers of individuals recalled due to a positive test were low, it is an important finding as there would be little benefit in performing widespread screening strategies if the populations targeted were not motivated in engaging with follow-up and treatment if required.

If long-term infection with viral hepatitis results in an increased burden of disease, the argument for widespread screening and early detection is strengthened. In the HepFree cohort, twenty percent of individuals diagnosed with chronic HCV had evidence of significant fibrosis, defined as fibroscan liver stiffness score eKPa >12.5, METAVIR 4, Ishak fibrosis score of greater than or equal to 5. In immigrant populations we suspect that in the majority of cases, viral hepatitis is acquired either vertically, or horizontally during the first few years of life. In the small HepFree cohort with chronic HCV, no correlation was identified between age, and therefore presumed duration of infection and the degree of fibrosis observed. One important finding that this analysis did identify though, was that there was evidence of advanced fibrosis in individuals infected with HCV and aged less than 30. It is difficult in these cases to determine whether the advanced degree of fibrosis was solely caused by HCV virus infection or a combination of factors, but this finding does support pre-existing research on fibrosis progression to cirrhosis after twenty years of infection (162, 169).

For the cohort of individuals diagnosed with HBV through HepFree, although relatively few individuals fulfilled the criteria for treatment, identifying the disease is beneficial for several reasons. Detection of the disease enables monitoring to be performed and this continued monitoring of viral load, liver function tests and degree of fibrosis enables adverse prognostic markers to be identified and modified by commencing antiviral therapy. In addition to this, disease detection enables contact tracing and screening of relatives and household contacts of the affected individual to be performed. For relatives and contacts that have negative contact tracing tests, a course of vaccinations can then be offered to reduce the risk of subsequent spread. This is especially important as currently in the UK, universal vaccination against HBV has not been adopted.

7. HepFree sub-study results

7.1 Introduction

Despite the traditional view that HCV is asymptomatic until an individual develops complications in the form of chronic liver disease, there is an increasing body of evidence exploring symptoms in individuals infected with the virus in the absence of cirrhosis. The major limitation of much of the pre-existing research is that it has been conducted in individuals aware of their diagnosis, and therefore results may be hindered by recall bias and the Hawthorne effect.

Anecdotal observations made of individuals infected with chronic HCV in an outpatient setting prompted me to design the Hep-Free observational sub-study. This was a retrospective case control study designed to investigate the impact of chronic HCV on healthcare utilisation. The sub-study allowed us to explore symptoms and episodes of care arising as a result of those symptoms in individuals who were not at that time aware if their hepatitis C status.

We hypothesised that compared to healthy individuals with no history of viral hepatitis infection, individuals with undiagnosed chronic HCV would have a greater number of attendances to primary care as a result of symptoms occurring secondary to the virus. We further hypothesised that evidence of prior infection with HCV, but no evidence of ongoing or active infection, would not result in greater use of primary care resources compared to healthy individuals.

7.2 Methods

With supervision from the HepFree trial CI, I designed and wrote the protocol for the sub-study and completed the IRAS form, a copy of the protocol is available in Appendix 14. Sub-study documents were reviewed by the Bart's Health NHS Trust Research Development team, Joint Research Management Office (JRMO), Queen Mary Innovation Centre, Lower Ground Floor, 5 Walden Street, London, E1 2EF and subsequently underwent internal peer review at the Blizard Institute, 4 Newark Street, London, City of London, E1 2AT. Provisional sponsorship was sought from the Joint Research Management Office for Bart's Health NHS Trust and Queen Mary University London, Mile End Road, London, E1 4NS. Once sponsorship had been agreed, trial documents were submitted for central ethics review to the London-West London & GTAC Research Ethics Committee, The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS. Following a committee meeting at the Hammersmith Hospital,

London, W12 0NN, central ethics approval was granted and Queen Mary University London subsequently provided full sponsorship. Once all agreements were in place, data collection began in all practices performing targeted testing in Bradford.

The sub-study included all individuals with a positive anti-HCV test that had consented to participate in the HepFree trial in Bradford between March 2014 and February 2016. Participants with a positive anti-HCV test (the cases) were divided into two groups dependent on the outcome of the RNA test. Controls were matched to cases using a 1:1 ratio and comprised of individuals that had consented to the HepFree trial and tested negative for both HBV and HCV.

Controls were identified by using the trial screening log and matched to cases using the following criteria:

- Age
- Gender
- Ethnicity
- Country of birth
- Duration of time residing in the UK.

In the event of more than one control being identified, the trial participant to be included was selected at random using Microsoft EXCEL random function.

The following cases were excluded from analysis:

- Participants with a positive test that failed to engage with subsequent trial related activities, also known as lost to follow up.
- Participants with anti-HCV positive status that had previously received anti-viral therapy for the treatment of chronic HCV.
- Participants that withdrew consent to continue in the HepFree trial.
- Participants that died during the trial follow-up period.

For the case-control study, participants were divided into four groups for analysis as follows:

- Group 1: Chronic HCV: anti-HCV positive, RNA positive.
- Group 2: Group 1 matched controls.
- Group 3: Evidence of previous HCV with spontaneous clearance: anti-HCV positive, RNA negative.
- Group 4: Group 3 matched controls.

Demographic data, in addition to clinical information of year on year GP attendances, was collected from SystmOne (S1). As described previously, S1 is a clinical computer system containing electronic patient records used in primary care. Data on each attendance was collected from the point of arrival in the UK, or from 1st January 2005 for individuals that had resided in the UK prior to this date.

During data collection, the clinical fellow (myself) reviewed each clinical encounter that had been recorded within the patient journal on S1. For the purposes of data collection, the diagnosis, or outcome of the clincal encounter was then coded, to enable analysis,using the Wonca Internation Classification Committee, International Classification of Primary Care Second Edition (ICPC), available in Appendix 15. This classification contains seventeen categories and was selected for use as it enables classification of the patient's reason for encounter, the problems or diagnoses that are present, in addition to general health care interventions that are routinely performed in primary care. The ICPC has been accepted within the WHO Family of International Classifications.

Descriptive analysis was carried out in Microsoft EXCEL and I was the sole contributor to this section of the results. Statistical analysis using the data was performed by an independent statistician with my assistance. Poisson and negative binomial based generalised linear models were fitted in STATA 14 using Generalised Estimating Equations with an autoregressive correlation matrix of order 1 (AR1). Relative risks were estimated using the univariate negative binomial model.

Statistical considerations

The HepFree sub-study was an exploratory study performed using individuals identified through the main HepFree trial. Given the small numbers of participants with a positive screening test for HCV, the sub-study was clearly underpowered and therefore all results obtained need to be interpreted with great caution.

An independent statistician was consulted with regards to a power calculation. They concluded that power could be calculated based on the number of appointments per year for each study group. The total number of appointments over the course of the study, per group, should converge to a normally distributed variable by the central limit theorem. Therefore the mean appointments per year also does. The size of N required for convergence is not known.

In Group 1, N=73.3 with sd = 52.7 and in Group 2, N=61.6 with sd = 46.1.

Using the inbuilt power function in STATA 15 (STATAcorp, college station, TX USA) we find a power of 12.3% assuming an alpha level of 0.05, with a required sample for 80% power of 283 per group and a required sample for 90% power of 377 per group.

7.3 Results

There were 108 participants included in the analysis; 54 individuals with either chronic HCV or evidence of previous infection with spontaneous eradication, and 54 healthy controls, individuals with no evidence of past or current infection with viral hepatitis. Tables 42-45 contain descriptors for participants in each group including age, gender, ethnicity, cumulative number of visits, interval of follow up and average number of visits per year for each participant. The column chart in Figure 37 demonstrates the number of participants by age group in each of the groups included in the analysis.

There were 31 participants in group 1; the cohort identified to have chronic HCV through testing in the HepFree trial. The cohort consisted of 18 females; median age 41, SD 15.6 and 13 males; median age 39, SD 11.3. 96% were first generation immigrants of Pakistani origin, and 3% (1/31) was second generation of British-Pakistani ethnicity. In this cohort, the total number of visits in 303 years of follow-up was 1622; 1150 appointments in 185 years of follow-up for females compared to 472 in 118 years of follow-up in males.

The cohort of healthy controls selected at random from all HepFree participants that fulfilled the matching criteria consisted of 18 females; median age 41, SD 15.7 and 13 males; median age 38, SD 11.4. The ethnic composition of group 2 was identical to that of group 1. In this cohort, the total number of appointments in 297 years of follow-up was 1569; 1158 appointments in 185 years of follow-up for females and 411 in 112 years for males.

Group 3 consisted of individuals with evidence of previous infection with HCV associated with spontaneous clearance. There were 23 participants in group 3; 18 females; median age 46.5, SD 11.2 and 5 males; median age 43, SD 11.8. The total number of years of follow-up was 210, and the total number of appointments 1686. The cumulative number of visits in female participants was 1417, in 159 years of follow-up compared to 269 appointments over 51 years in males. The ethnic composition of this group was marginally more diverse; 78% were of Pakistani origin, 9% (2/23) were second generation British Pakistani and the remaining participants were of Bangladeshi, Black African and Polish descent.

The healthy controls in group 4 were closely matched to group 3; 18 females; median age 46.5, SD 11 and 5 males; median age 41, SD 12.1. In 208 years of follow-up, participants had accessed services in primary care on 1417 occasions; females 979 in 158 years of follow-up

and males, 438 in 50 years of follow-up. Due to significant difficulties in matching participants using the criteria set out in Materials and Methods, the ethnic composition of group 4 varied slightly from group 3; 13% (3/23) of participants were of British Pakistani ethnic origin.

In summary, the majority of the total study population were of Pakistani origin, and female; 88% and 65% respectively. The mean age of participants in groups 1 and 2 was lower than in groups 3 and 4; 43 years versus 48 years (Table 46). The breakdown of participants included in the sub-study by gender and age group is demonstrated in Figure 38.

Participants in groups 3 and 4 provided 210 and 208 patient years of data compared to 303 and 297 for groups 1 and 2. The number of attendances observed per patient was higher in groups 3 and 4 as demonstrated in the pie chart in Figure 39. The total number of recorded appointments per patient ranged from 0-42 in a single year and from 2-230 overall. Follow up for participants ranged from 1-12 years.

Expected trends in the usage of GP services were seen in all age groups and for female patients compared to males. The year on year attendance was proportionally increased for age groups 41-65 and 65 years and over when compared to the baseline age group 18-40 (Table 47). The data shows that attendance for people of Bangladeshi ethnicity was greater than of Pakistani ethnicity, with Bangladeshi patients having mean usages of 144.5 (Table 48). It is important to note however the very small sample size on which this comparison was made, Bangladeshi patients n=2.

Table 42: HepFree sub-study group 1 participant characteristics

Table 42 contains descriptors for participants in group 1 (individuals with chronic HCV) including age, gender, ethnicity, cumulative number of visits, interval of follow up and average number of visits per year.

Participant	Gender	Age	Ethnicity	Total no. of visits to the GP	Years of follow-up	Average visits/yr
1	F	33	Pak	85	11	7.7
2	F	42	Pak	116	10	11.6
3	F	40	Pak	134	11	12.2
4	F	83	Pak	115	10	11.5
5	F	47	Pak	35	11	3.2
6	M	48	Pak	51	11	4.6
7	F	51	Pak	55	10	5.5
8	F	71	Brit-Pak	103	10	10.3
9	M	32	Pak	11	11	1.0
10	F	46	Pak	36	10	3.6
11	F	51	Pak	111	10	11.1
12	F	30	Pak	65	10	6.5
13	M	73	Pak	40	11	3.6
14	M	41	Pak	33	11	3.0
15	F	29	Pak	48	10	4.8
16	M	47	Pak	160	10	16
17	M	37	Pak	64	11	5.8
18	M	43	Pak	27	11	2.5
19	F	38	Pak	40	11	3.6
20	F	23	Pak	13	11	1.2
21	F	49	Pak	27	11	2.5
22	F	37	Pak	35	11	3.2
23	F	28	Pak	56	9	6.2
24	F	38	Pak	35	8	4.4
25	M	35	Pak	28	8	3.5
26	M	40	Pak	10	9	1.1
27	M	27	Pak	21	2	10.5
28	F	69	Pak	41	11	3.7
29	M	39	Pak	3	6	0.5
30	M	27	Pak	2	5	0.4
31	M	36	Pak	22	12	1.8
Total	**31**			**1622**	**303**	**5.3**
Abbreviations- **Pak**: Pakistani ethnic origin; **Brit-Pak**: British Pakistani ethnic origin						

Table 43: HepFree sub-study group 2 participant characteristics

Table 43 contains descriptors for participants in group 2 (healthy controls matched to group 1) including age, gender, ethnicity, cumulative number of visits, interval of follow up and average number of visits per year.

Participant	Gender	Age	Ethnicity	Total no. of visits to the GP	Years of follow-up	Average visits/yr
32	F	32	Pak	60	10	6.0
33	F	40	Pak	17	10	1.7
34	F	83	Pak	178	11	16.2
35	F	52	Pak	63	10	6.3
36	F	71	Pak	84	10	8.4
37	M	32	Brit-Pak	27	11	2.5
38	F	46	Pak	84	11	7.6
39	F	30	Pak	36	10	3.6
40	M	40	Pak	22	11	2.0
41	F	29	Pak	34	11	3.1
42	M	47	Pak	50	10	5.0
43	M	36	Pak	44	10	4.4
44	F	38	Pak	55	11	5.0
45	F	50	Pak	37	11	3.4
46	F	36	Pak	46	10	4.6
47	F	28	Pak	105	10	10.5
48	F	38	Pak	20	7	2.9
49	M	34	Pak	21	8	2.6
50	M	39	Pak	32	7	4.6
51	M	27	Pak	6	2	3.0
52	F	47	Pak	84	11	7.6
53	F	22	Pak	46	10	4.6
54	M	47	Pak	18	11	1.6
55	F	42	Pak	73	11	6.6
56	F	51	Pak	28	11	2.5
57	F	68	Pak	108	10	10.8
58	M	43	Pak	31	10	3.1
59	M	74	Pak	112	10	11.2
60	M	38	Pak	13	5	2.6
61	M	28	Pak	16	6	2.7
62	M	36	Pak	19	11	1.7
Total	**31**			**1569**	**297**	**5.3**
Abbreviations- **Pak**: Pakistani ethnic origin; **Brit-Pak**: British Pakistani ethnic origin						

Table 44: HepFree sub-study group 3 participant characteristics

Table 44 contains descriptors for participants in group 3 (spontaneous clearance of HCV) including age, gender, ethnicity, cumulative number of visits, interval of follow up and average number of visits per year.

Participant	Gender	Age	Ethnicity	Total no. of visits to the GP	Years of follow-up	Average visits/yr
63	F	33	Pak	29	10	2.9
64	F	53	Pak	55	10	5.5
65	F	71	Pak	176	10	17.6
66	F	38	Brit-Pak	88	10	8.8
67	M	58	Pak	92	11	8.4
68	M	61	Bangladeshi	59	11	5.4
69	F	44	Pak	60	10	6.0
70	F	50	Pak	126	10	12.6
71	F	37	Pak	91	10	9.1
72	F	45	Pak	42	11	3.8
73	F	44	Pak	133	10	13.3
74	F	50	Pak	216	10	21.6
75	F	62	Pak	117	10	11.7
76	F	73	Pak	47	10	4.7
77	M	38	Pak	15	7	2.1
78	F	40	Pak	3	1	3.0
79	F	44	Black African	31	5	6.2
80	M	43	Polish	46	10	4.6
81	F	56	Pak	42	8	5.3
82	F	48	Pak	67	11	6.1
83	F	35	Pak	87	11	7.9
84	M	30	Brit-Pak	57	12	4.8
85	F	59	Pak	7	2	3.5
Total	**23**			**1686**	**210**	**8.0**
Abbreviations- **Pak**: Pakistani ethnic origin; **Brit-Pak**: British Pakistani ethnic origin						

Table 45: HepFree sub-study group 4 participant characteristics

Table 45 contains descriptors for participants in group 2 (healthy controls matched to group 3) including age, gender, ethnicity, cumulative number of visits, interval of follow up and average number of visits per year.

Participant	Gender	Age	Ethnicity	Total no. of visits to the GP	Years of follow-up	Average visits/yr
86	F	34	Pak	51	10	5.1
87	F	53	Pak	51	10	5.1
88	F	38	Brit-Pak	43	10	4.3
89	F	45	Pak	33	10	3.3
90	F	50	Pak	61	10	6.1
91	F	37	Pak	43	11	3.9
92	F	44	Pak	102	10	10.2
93	F	49	Pak	63	10	6.3
94	F	72	Pak	90	10	9.0
95	M	39	Pak	80	8	10.0
96	F	40	Pak	2	1	2.0
97	M	61	Bangladeshi	230	11	20.9
98	F	71	Pak	108	10	10.8
99	M	58	Pak	42	11	3.8
100	F	61	Pak	47	10	4.7
101	F	54	Pak	42	8	5.3
102	F	46	Pak	85	11	7.7
103	F	47	Pak	68	10	6.8
104	F	41	Black African	10	5	2.0
105	F	35	Brit-Pak	74	10	7.4
106	M	41	Polish	41	10	4.1
107	M	29	Brit-Pak	45	10	4.5
108	F	59	Pak	6	2	3.0
Total	**23**			**1417**	**208**	**6.3**
Abbreviations- **Pak**: Pakistani ethnic origin; **Brit-Pak**: British Pakistani ethnic origin						

Table 46: Descriptive analysis of case control participants

The characteristics of cases and controls selected for the HepFree sub-study. The majority of the study population were female 66.67% versus 33.33%. The mean age of participants in groups 1 and 2 was lower than in groups 3 and 4; 43 years versus 48 years.

No. of patients		% Male	% Female	Age range (years)	Mean age (sd)	Cumulative visits	Patient years	Mean cumulative visit/pt (sd)
N = 108		33.33	66.67	22-83	45.1 (13.4)	6294	1018	58.3 (44.2)
N by group								
1. Chronic HCV: Ab pos, RNA pos	31	41.94	58.06	23-83	42.9 (14.4)	1622	303	52.3(40.6)
2. Healthy controls to group 1	31	41.94	58.06	22-83	42.7 (14.5)	1569	297	50.6(38)
3. Previous HCV: Ab pos, RNA neg	23	21.74	78.26	30-73	48.3 (11.7)	1686	210	73.3(52.7)
4. Healthy controls to group 3	23	21.74	78.26	29-72	48 (11.6)	1417	208	61.6(46.1)
Abbreviations - **Ab pos**: Anti-HCV positive; **RNA pos**: RNA test for chronic HCV positive								

Table 47: GP usage by age and disease status

A table of GP services usage by individuals in each age group. There was an increased use of services by individuals of advancing age and by females compared to males.

	No. of pts (%)		No. of appointments per pt (No. of patients)			
Appointments per patient by age group (no. patients)	Male	Female	Group 1	Group 2	Group 3	Group 4
18-40	21 (19.4)	28 (25.9)	39.5 (17)	34.4 (18)	52.9 (7)	48.3 (7)
41-65	13 (12.0)	34 (31.5)	65.1 (10)	52.0 (9)	78.1 (14)	62.9 (14)
65 and over	2 (1.9)	10 (9.3)	74.8 (4)	120.5 (4)	111.5 (2)	99 (2)
Abbreviations – **No**.: number; **pt**: patient						

Table 48: GP usage by ethnic group

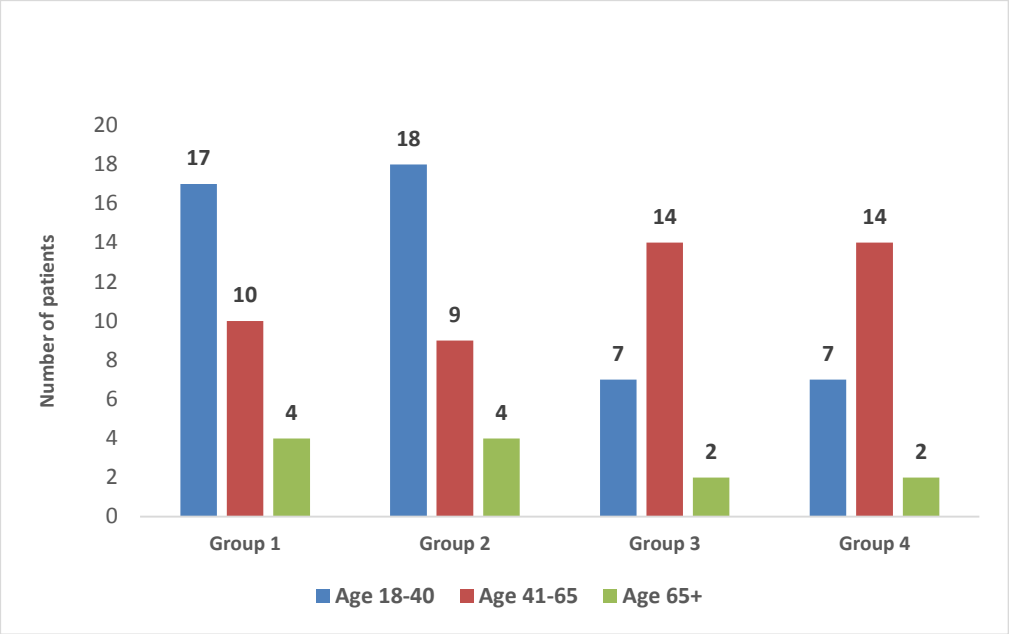
GP service usage by individuals included in the sub-study according to ethnicity. Individuals of Bangladeshi ethnicity accessed GP services more frequently compared to all other ethnicities. Note small sample size; Bangladeshi patients n=2.

Number of patients by ethnicity, age and study group	Overall (% of total)	Group 1	Group 2	Group 3	Group 4	18-40	41-65	65 and over	Mean cumulative GP visits (sd)
Pakistani	95 (88)	30 (96.8)	30 (96.8)	18 (58.1)	17 (54.8)	42 (86)	41 (87)	12 (100)	58.2 (42.7)
Brit-Pakistani	7 (6.5)	1 (3.2)	1 (3.2)	2 (6.5)	3 (9.7)	7 (14)	0 (0)	0 (0)	49.3 (26.4)
Bangladeshi	2 (1.9)	0 (0)	0 (0)	1 (3.2)	1 (3.2)	0 (0)	2 (4.3)	0 (0)	144.5 (120.9)
Black African	2 (1.9)	0 (0)	0 (0)	1 (3.2)	1 (3.2)	0 (0)	2 (4.3)	0 (0)	20.5 (14.8)
Polish	2 (1.9)	0 (0)	0 (0)	1 (3.2)	1 (3.2)	0 (0)	2 (4.3)	0 (0)	43.5 (3.5)

Figure 37: The ages and disease status of participants included in the sub-study

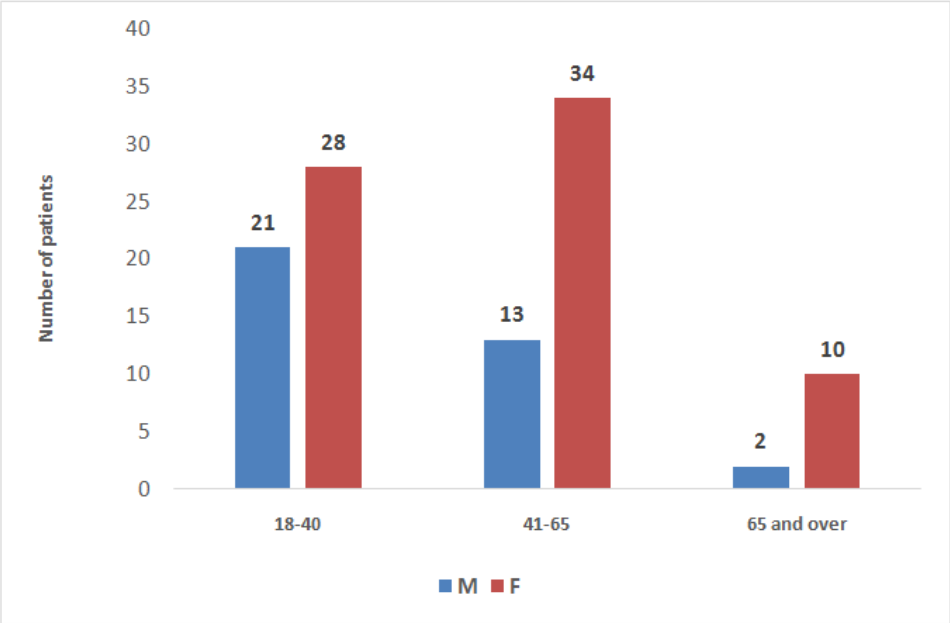
In the following Figures, the definitions of the groups are listed below:

- Group 1: Chronic HCV: anti-HCV positive, RNA positive
- Group 2: Matched healthy controls for Group 1.
- Group 3: Evidence of previous HCV: anti-HCV positive, RNA negative.
- Group 4: Matched healthy controls for Group 3.



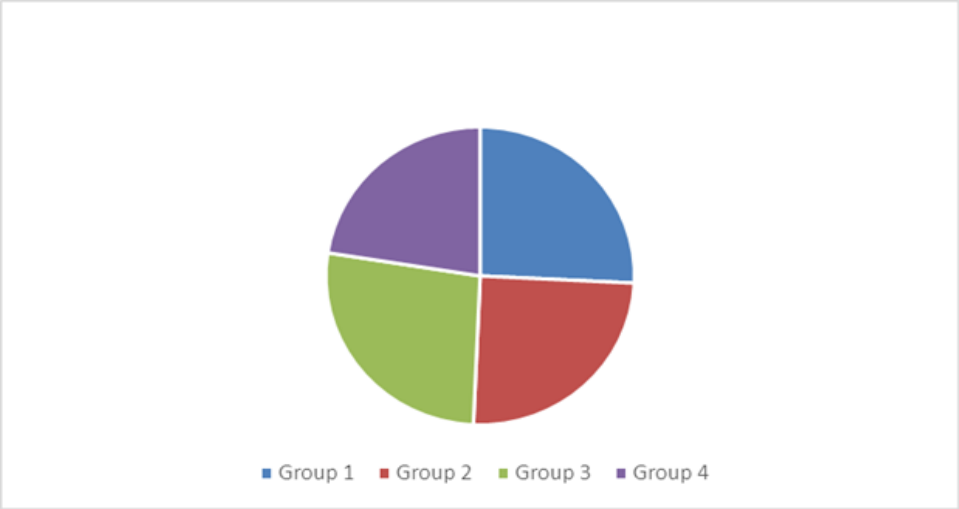
A column chart detailing the ages of participants included within the four groups of the sub-study. Cases and controls between groups 1 and 2, and 3 and 4 were closely matched in terms of age.

Figure 38: The range of ages and genders of participants included in the sub-study



A column chart detailing the ages and genders of participants included in the sub-study. The small sample size of men over the age of 65 makes it difficult to draw any conclusions about healthcare utilisation in this group.

Figure 39: GP service usage by each sub-study group



A pie-chart of GP attendances by each group included in the sub-study. The number of attendances observed per patient was higher in groups 3 and 4 (anti-HCV positive, RNA negative and controls) compared to groups 1 and 2 (RNA positive chronic HCV and controls).

Details pertaining to each episode of care for all male and female participants included in the sub-study are demonstrated in Tables 49 and 50 and a column chart displaying the cumulative number of appointments for each ICPC category is shown in Figure 40. Independent of gender and disease status, attendance for a process or procedure was the most commonly coded reason for an episode of care; 25.6% of all attendances in men were for this indication and 23.8% of attendances in women.

Attendances related to the musculoskeletal system were high in all cohorts. In the HCV infected cohort, attendance with a musculoskeletal system related problem was the second most common reason for attendance in both males and females; 17.8% of attendances and 13.0% of attendances respectively. Attendances for this indication in the HCV infected cohorts were slightly higher than in the healthy control groups; 15.8% and 12.1%, but this was non-significant, X^2 *(1) = 1.13, p=.288.* A high number of attendances for this indication were also observed in the previously infected HCV cohort in both males and females; 13.7% and 16.1% respectively.

In the HCV infected male cohort, 17.2% of attendances were coded as endocrine related, compared to 1.0% in the healthy control group. Attendances for this reason were significantly higher in HCV infected males compared to those with evidence of previous infection with spontaneous clearance; X^2 *(1) = 25.2, p=<.001.*

Episodes of care relating to pregnancy, child-bearing and family planning were more frequently observed in the HCV infected cohort and their matched healthy controls, compared to individuals with evidence of previous infection and their controls; 4.8% of attendances versus 2.7%. This difference is likely to be related to the mean ages of the two sets of cohorts in the comparison.

In females, presentations with psychological complaints occurred more frequently in healthy control participants compared to individuals with undiagnosed chronic HCV; 4.8% versus 2.5%.

Table 49: ICPC coded attendance outcomes for male participants

Details of each episode of care in male participants included in the sub-study, coded using the ICPC. Healthcare utilisation by males in group 4 (healthy controls matched with group 3) was far greater; total number of attendances 438 versus 269, and individuals in this group frequently presented with complaints related to the digestive system 68 versus 18, and respiratory system 77 versus 29. 17% of attendances in individuals with chronic HCV related to the endocrine system.

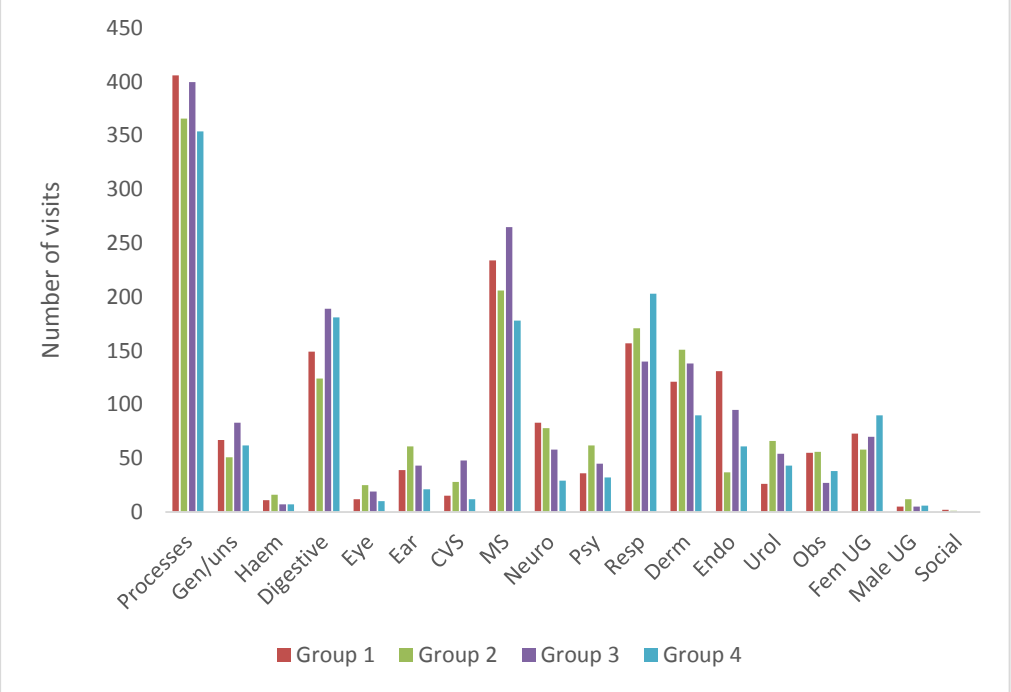
	Group 1	Group 2	Group 3	Group 4
Total number of males, N=36	13	13	5	5
Total number of attendances: 1590	472	411	269	438
ICPC code				
Process codes	94	111	74	128
General and unspecified	13	10	7	8
Blood, blood forming organs and immune mechanism	0	3	0	2
Digestive	39	36	18	68
Eye	3	1	1	2
Ear	8	12	3	10
Cardiovascular	0	10	22	6
Musculoskeletal	84	65	37	56
Neurological	42	17	6	6
Psychological	7	6	15	5
Respiratory	42	54	29	77
Skin	51	59	37	26
Endocrine/metabolic and nutritional	81	4	12	33
Urological	3	11	3	5
Pregnancy, childbearing, family planning	0	0	0	0
Female genital	0	0	0	0
Male genital	5	12	5	6
Social problems	0	0	0	0

Table 50: ICPC coded attendance outcomes for female participants

Details of each episode of care in female participants included in the sub-study, coded using the ICPC. The total number of attendances by females in groups 1 and 2 were very similar, 1150 versus 1158. Attendances to primary care for procedures were high in all groups independent of disease status, as were attendances for disorders relating to the musculoskeletal system, digestive system and respiratory system.

	Group 1	Group 2	Group 3	Group 4
Total number of females, N=72	13	13	5	5
Total number of attendances: 4704	1150	1158	1417	979
ICPC code				
Process codes	312	255	326	226
General and unspecified	54	41	76	54
Blood, blood forming organs and immune mechanism	11	13	7	5
Digestive	110	88	171	113
Eye	9	24	18	8
Ear	31	49	40	11
Cardiovascular	15	18	26	6
Musculoskeletal	150	141	228	122
Neurological	41	61	52	23
Psychological	29	56	30	27
Respiratory	115	117	111	126
Skin	70	92	101	64
Endocrine/metabolic and nutritional	50	33	83	28
Urological	23	55	51	38
Pregnancy, childbearing, family planning	55	56	27	38
Female genital	73	58	70	90
Male genital	0	0	0	0
Social problems	2	1	0	0

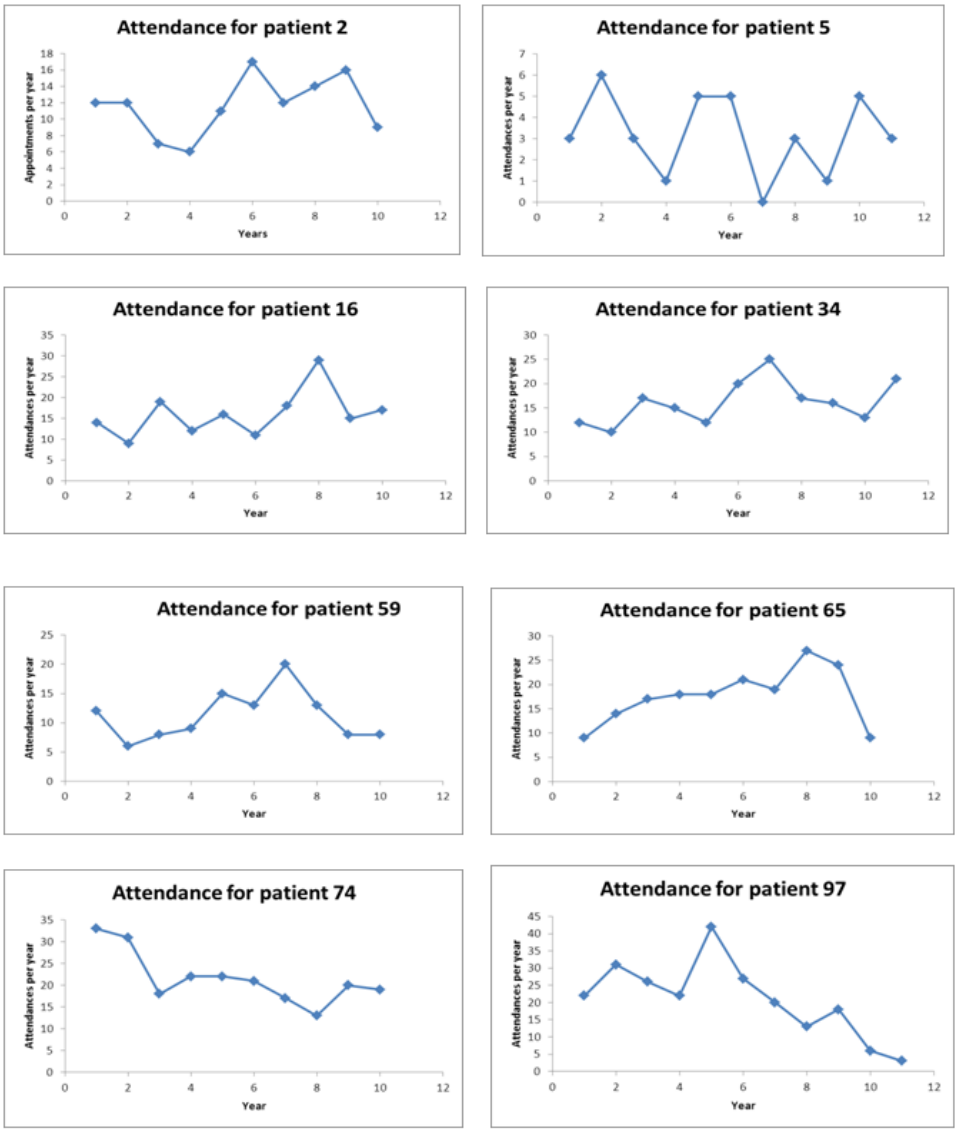
Figure 40: ICPC category for each episode of care according to disease status



A column chart detailing the frequency of attendances attributed to each ICPC category in the four groups of participants included in the sub-study. As demonstrated in Tables 49 and 50, episodes of care relating to a process/procedure been performed were high, independent of disease status.

Figure 41: Time series plots of attendances for selected patients

Figure 41 contains time series plots of attendances for participants included in the HepFree sub-study, selected at random using the random function within EXCEL. No discernible pattern was identified.



The year-on-year attendance was proportionally increased for age groups 41-65 and 65 and over compared to the baseline of age 18-40 (Table 51), for female patients compared to male, for Bangladeshi ethnicity vs Pakistani (limited data), and for anti-HCV positive, RNA negative versus control patients. 95% Confidence intervals for these estimates that do not include the value 1 might be considered statistically significant at the 5% level.

7.4 Regression model fitting

Plots of the participant level variance vs mean (appointments per year) suggest that no single value of k adequately expresses the relationship var ~mean^k for this data (Figure 42). Poisson GEE models including the covariates of age, ethnicity, gender and group (pairwise 1 vs 2, 3 vs 4) showed a dispersion parameter of ~3.9.

Poisson GEE regression models therefore show over dispersion. Negative binomial models (dispersion parameter 0.6) with all fitted covariates and robust standard errors (Table 52) showed that anti-HCV positive participants had 24% more visits to their GP year-on-year when adjusted for other available factors. This difference was not statistically significant at the 5% level. The statistical significance of these results was found to be sensitive to the choice of correlation matrix although convergence problems occur.

Figure 42: A plot of the patient level variance versus mean number of appointments per year

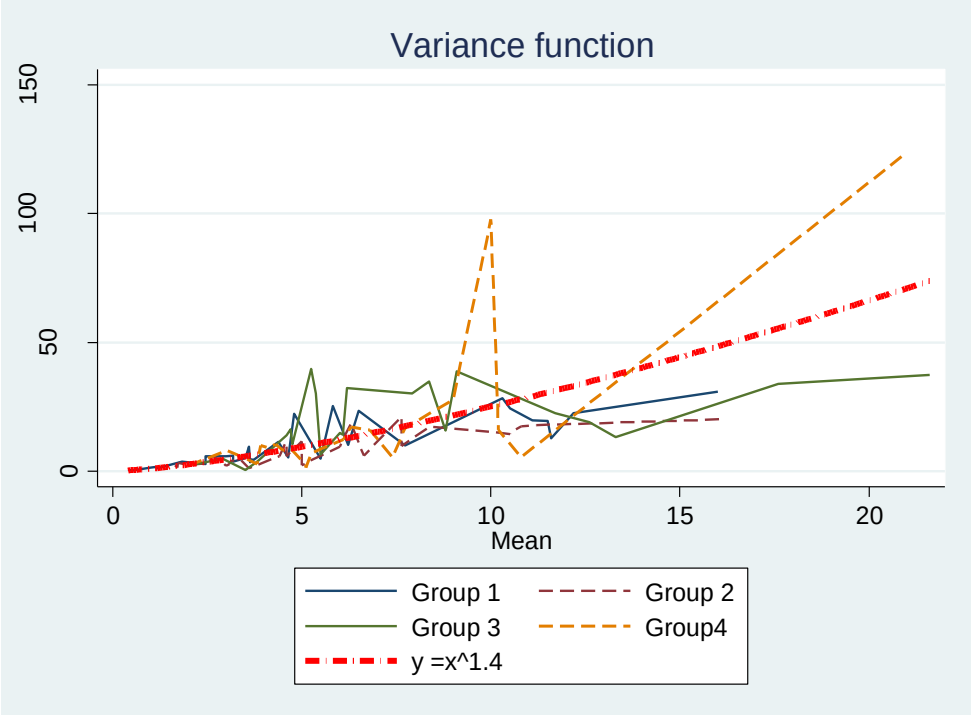


Table 51: Cluster adjusted proportional differences in attendance estimates for model parameters.

Appointments per year	Relative risk estimate	95% confidence interval	
		Lower estimate	Upper estimate
Age group baseline for comparison = 18-40			
Age 41-65	10480	1.137	1.926
Age 65 and over	2.124	1.564	2.884
Ethnicity: Compared to Pakistani			
British Pakistani	0.785	0.502	1.229
Bangladeshi	1.984	0.829	4.744
Black African	0.653	0.353	1.208
Polish	0.690	0.598	0.796
Gender : Compared to male			
Female	1.487	1.065	2.0741
Group			
Group 3 (HCV Ab pos) vs Group 4 (Control patients)	1.217	0.842	1.758
Group 1 (HCV RNA pos) vs Group 2 (control patients)	1.000	-	-

Table 52: Parameter estimates for Generalised Estimate Equation model fitting, expressed as relative risk.

Dependent variable =number of appointments per year per participant	Parameter estimate	Standard Error	P value	95% CI lower estimate	95% CI upper estimate
Age group Baseline is 18-40					
40-65	1.26	0.25	0.25	0.85	1.87
65 and over	1.71	0.49	0.06	0.98	2.99
Gender Baseline is male.					
Female	1.19	0.26	0.42	0.78	1.82
Ethnicity Baseline is Pakistani					
Brit Pakistani	1.05	0.28	0.86	0.62	1.78
Bangladeshi	2.14	0.78	0.04	1.05	4.38
Black African	0.45	0.21	0.09	0.18	1.14
Polish	0.64	0.25	0.27	0.30	1.40
Group 3: HCV Ab +ve group	1.24	0.17	**0.124**	0.94	1.63
Constant term	4.49	1.15	0.00	2.72	7.41

7.5 Discussion

The HepFree sub-study was designed to explore the impact of undiagnosed chronic HCV on utilisation of healthcare resources. Given the extensive body of research that already exists, we hypothesised that individuals with chronic HCV will access healthcare services in primary care more frequently than uninfected 'healthy' individuals that have similar characteristics.

Previous research, in addition to identifying that irrespective of the degree of histological severity, individuals with HCV feel unwell, has made an association between SVR and symptomatic relief in turn resulting in an increased QOL. With this in mind, in the sub-study we included a cohort of individuals with evidence of previous infection with HCV associated with spontaneous viral clearance and compared healthcare usage in this group with healthy individuals.

The sub-study was a retrospective case-control design. Information pertaining to previous attendances was collected from individual patient electronic records stored on clinical computer systems within GPs. The demography of the sub-study population was largely reflective of that seen in the main HepFree trial. Overall, 67% of participants were female and of the total study population, 88% were first generation immigrants of Pakistani origin. In the HepFree trial, testing rates in this ethnic group were far higher than others, with 37% of eligible and invited individuals consenting for testing.

As a proportion of the total number of males included in the sub-study, nearly three quarters were in cohort 1, comprising 42% of the cohort population, compared to in cohort 3 where males only made up 22% of the population. This finding is likely to be related to the impact of gender on spontaneous viral clearance.

The number of attendances observed in cohorts 3 and 4; spontaneous viral clearance and healthy controls were higher than in cohorts 1 and 2; chronic HCV and matched healthy controls. This finding may be explained by the increase in the median ages of the two sets of cohorts being compared, especially as year on year attendance in the study was found to be increased for age groups 41-65 and 65 years and older compared to the baseline group aged 18-40. This observation is consistent with the theory that migrants are usually both young and healthy on arrival but their health deteriorates with increasing duration of residence.

Although the majority of migrants have both lower socioeconomic status as well as poorer access to healthcare in their country of birth, on arrival in their host nation, migrants are usually relatively healthy and this finding is attributed to the process of self-selection that occurs prior to migration. However, likely as a consequence of both cultural and behavioural changes in the host country, migrant heath deteriorates in relation to duration of stay (336,337).

Due to the small number of non-Pakistani individuals included in the sub-study it is difficult to draw any meaningful conclusions relating to healthcare usage according to ethnicity.

In all cohorts examined in the sub-study, attendance rates were higher in females compared to males and there are several possible explanations for this finding. Firstly, women are invited to participate in more preventative screening strategies compared to males, and most of these take place in primary care. The second reason may be that females often require more primary care appointments for consultations related to family planning, contraception and pregnancy. Thirdly, migrant females tend to have a lower self-perception of their general health compared to native females and males of all ethnicities. Finally, and perhaps most pertinent to the characteristics of the cohorts being studied is the psychological impact of immigration on health perception and health related anxiety. Loneliness and isolation is prevalent amongst immigrant populations, and is probably increased in female immigrants. Environmental and cultural differences make it difficult for immigrants to settle into communities and this is often made worse by a language barrier. Upon migrating, individuals are separated from families and therefore support networks, and are often responsible for raising the children due to work commitments of male immigrants. This combination of loneliness and isolation can result in depression and possible somatisation. A case-control study exploring the characteristics of frequent attenders found that low educational qualifications and a poor QOL were associated with healthcare usage (338).

Independent of gender and disease status, attendances for a process or procedure were the most commonly coded reasons for an episode of care, with nearly one quarter of all attendances being for this indication in both males and females.

Of particular interest, because of the findings of previous research was the frequency of attendances for problems related to the musculoskeletal system. Attendances for MSK problems were prevalent in all cohorts. In cohort 1, in both males and females, attendances for this indication were the second most common reason to consult a primary care practitioner. In the HCV infected cohort, attendances for this indication occurred slightly more frequently than in the non-infected cohort, but this was non-significant, $X^2 (1) = 1.13, p=.288.$

The HepFree sub-study failed to identify an increase in healthcare usage in cohorts of individuals with chronic HCV compared to age and sex matched healthy controls. Possible reasons for this are discussed in detail in 8.6 HepFree sub-study discussion.

8. HepFree discussion

8.1 Introduction

The HepFree trial was designed to determine whether a universal screening programme for viral hepatitis should be designed and offered to first and second generation immigrants living in England. My role in this national study was to develop and manage the Bradford site. In this thesis I have presented the work that I completed in Bradford in addition to my own analysis of the Bradford data. This analysis will be used to inform and develop the analysis of the entire study. In addition I present work from my independent sub-study within the HCV cohort.

The study had three broad aims; firstly to examine the feasibility and acceptability of targeted testing for viral hepatitis in first and second generation immigrants in primary care, using pre-existing databases to identify the target population. The second aim was to establish the most effective method of inviting immigrants to attend for testing and finally to gain information on the prevalence of viral hepatitis in immigrant populations living in specific locations in England. A better understanding of how to identify, approach and engage ethnic minority groups that are at risk of viral hepatitis will help us to successfully diagnose and treat those infected individuals.

Currently, for HCV, the end goal of testing and identification of infected individuals is treatment with subsequent viral eradication, otherwise known as SVR. For HBV, the end goal of testing is identification of those individuals at risk of HBV associated complications including HCC and to commence treatment in those individuals.

At the time of inception, there were no known active studies that were identifying their target population using demographic data stored within electronic medical records in primary care, nor had widespread case-finding for viral hepatitis in first and second generation immigrants using letter invitation been performed in primary care before. The strengths of this study were the large scale of the trial with engagement from diverse regions within England and the major weakness with the study was the rapidly changing environment (both in NHS systems and structures and the development of new drugs).

8.2 Review of the Bradford case-finding results

At the point that data was collected to produce this thesis, ten practices had completed eighteen months of targeted testing, and data from those practices was included in the analysis. A total of 7,302 eligible participants had participated in the trial, representing a testing rate of 35.7% of the total eligible population that had received an invitation to participate. The study population consisted of 4173 (57.1%) females and 3123 (42.8%) males. As a proportion of the total eligible population, testing occurred in 37.1% of females and 29% of males.

Attendance and engagement in HepFree was lower than attendance at pre-existing national screening programmes in England, but was higher than previous European viral hepatitis case-finding projects conducted in immigrant populations.

Attendance data for national screening programmes in the UK is presented as screening coverage. This is defined as the percent of the population that are eligible for screening at any given point in time that have been screened adequately within the specified period set out by the screening programme. In 2014/15, screening coverage rates for breast cancer, cervical cancer and bowel cancer were 75.1%, 73.5% and 58.2% respectively. These figures are considerably higher than the observed testing rates in our trial. Difficulty arises however in attempting to compare screening rates for these pre-existing screening programmes with HepFree, mainly because of the significant variations in the target populations. In HepFree, the eligible population consisted solely of ethnic minority individuals.

Historically, an association has been demonstrated between migrant populations and lower or non-attendance at screening programmes (339-342). In the study by Webb et al, researchers in Manchester accessed the electronic screening records of all women eligible to participate in cervical screening in order to assess the rate of attendance according to both ethnicity and country of birth (339). In their data set, 9.3% of women were of south Asian ethnicity. Within this cohort, screening was performed significantly less frequently; 69.5% compared to 73% in the non-Asian cohort, p =<.0001 (339). In addition to lower screening rates observed in the south Asian cohort, a higher proportion of individuals within this group had never attended for screening compared to individuals from other ethnic groups, 14.7% versus 10.3% (339). The study also explored attendance at screening according to country of origin. Here a steep decline in the numbers screened was identified in individuals originating

outside of the UK; 57.4% versus 75.6%. In the cohort of individuals originating from outside the UK, nearly one third had never attended for screening, compared to 7.9% of UK nationals (339).

Recruitment to HepFree was greater than in other 'opt-in' viral hepatitis case-finding projects conducted in immigrant populations in Turkey and the Netherlands, and was comparable to bowel cancer screening rates in ethnically diverse postcodes in the UK (303,304,331,342).

The highest rates of participation in viral hepatitis case-finding campaigns have been observed in an antenatal setting (343,344). Multiple factors, discussed below may account for the differences observed in this specific population. In the antenatal setting, higher rates of engagement may have been observed because of the homogeneity of the trial population; individuals targeted by these trials were likely to behave in the same way. In addition to this, the psychological impact of a potential diagnosis may be more profound in these cohorts of individuals. Thoughts pertaining to how viral hepatitis might either affect their off-spring, or impact on their future health which would in turn impact on their ability to care for their off-spring may explain the increased level of engagement observed. Convenience sampling may also have impacted on trial participation as well. In the antenatal targeted testing trials, women were already engaged with medical services, undergoing 'standard of care' investigations, therefore if additional blood tests required for the trial could be taken at the same time as standard investigations, meaning no additional effort was required on the part of the participant then they may have been more inclined to participate in testing.

It was unsurprising that a higher proportion of female participants were tested through HepFree compared to males; there are several possible explanations for this. It is a common observation that higher rates of unemployment exist among ethnic minority females, therefore attendance at the GP surgery to participate in the trial would have been easier. It is also plausible that in the absence of time constraints associated with employment, this group of individuals would have more time available to socialise and may therefore be encouraged to attend for testing by peers and friends. In addition to these factors, it is well recognised, that with the exception of extremes of age, females attend appointments in primary care more frequently than males. This occurs for a variety of reasons including attendance for other preventative screening programmes, for consultations related to family planning and pregnancy, and also because of a difference in self-perception of their state of health (334,335). Irrespective of the reason for attendance, the increased frequency of

appointments increases the number of opportunities available for opportunistic testing to be conducted by staff within the practice. The gender discrepancy in attendance observed in HepFree has been identified in previous community based targeted testing programmes conducted in locations other than mosques (303,304,331).

In Bradford, trial participation and viral hepatitis testing occurred more frequently in first generation immigrants compared to second generation;72.8% versus 25.7% respectively. This finding is consistent with previous viral hepatitis case-finding studies conducted in immigrant populations (301,303,304,331,332). In HepFree, similar to other studies, higher rates of engagement with viral hepatitis testing were observed in individuals of advancing age. This is likely to have impacted on the proportions of first and second generation immigrants tested as first generation immigrants are more likely to be older (303,304,331).

Previous studies have investigated the effectiveness of different recruitment strategies on engagement with screening programmes. One study evaluating the use of different strategies to increase participation in colorectal cancer screening observed that participation was greater in both individuals that had consulted a clinician prior to screening, and in those that had received an information leaflet about the process in addition to their invitation letter (345). Another study demonstrated the positive effect of clinician endorsed invitation on participation in bowel cancer screening (346). These findings were taken into account during the trial design phase of HepFree, so in addition to participant information sheet, all eligible participants received an invitation letter that had been countersigned by their own clinician in addition to the trial CI. In addition to this, during the SIV, training was delivered to clinical staff within the practice encouraging them to give all eligible potential study participants the opportunity to discuss testing for viral hepatitis each time they attended the surgery.

From analysing the length of time between the invitation letter been sent and recruitment to the trial, data suggested that recruitment in HepFree was predominantly via an opportunistic approach. In order to perform this analysis, the assumption was made that if consent and testing occurred either on the same day that the invitation letter was given to an individual, or more than thirty-one days after the invitation letter had been generated and dispatched by the GP practice, then recruitment was not associated with the letter invitation. Using this assumption, 18.6% of accruals for HepFree were attributed to the letter invitation, with 81.3% of cases recruited by the opportunistic approach.

We do however recognise flaws associated with adopting this assumption. In real life, cultural, social and economic factors, in addition to first-hand experience of the consequences of hepatitis may all impact on a person's decision regarding participation in testing; not simply the timing of an invitation letter or a single discussion with a healthcare professional. Therefore, although in the majority of cases, the letter may not have been the sole driving force prompting an individual to book an appointment for testing; it may have contributed to their decision to participate in some way.

In view of this we do not feel that the results of this study alone are powerful enough to conclude that letter invitation is ineffective in future screening programmes directed at immigrants. Future research directly assessing the impact of letter invitation versus opportunistic invitation on engagement would help to either validate or refute these findings.

In the trial population in Bradford, the overall prevalence of viral hepatitis was 1.77%. 68 participants tested positive for HCV; 40 females and 28 males, and 61 cases tested positive for HBV; 23 females and 38 males. All participants with a positive hepatitis test were invited to be reviewed in a secondary care outpatient clinic. All participants with a positive anti-HCV test underwent further testing to detect RNA in order to diagnose chronic infection that would be amenable to treatment. In 18/68 cases, participants had previously received antiviral therapy for the treatment of HCV and there was no evidence of recurrence of disease in this cohort. RNA positive chronic HCV was identified in 25 cases and spontaneous viral clearance had occurred in the remaining 25 cases. One participant tested positive for both anti-HCV and HBsAg. In 91.4% of cases, participants were first generation, and 82% of cases originated in people born in countries in Asia-Pacific.

Due to the overall testing rate in Bradford been low, it is difficult to generalise the results of the HepFree trial and make assumptions about the prevalence of disease in the larger immigrant population residing in this area of England. It is difficult to establish whether the prevalence results obtained from HepFree truly reflect both the disease rate and associated burden of viral hepatitis in immigrant populations in Bradford, or whether they are representative of the prevalence of viral hepatitis in a self-selected healthy volunteer cohort that attended and participated in the trial. Previous research in general practice has demonstrated that populations that are 'less healthy' and have risk factors for disease are less likely to participate in screening programmes and if they do participate are more likely to drop out after displaying an initial interest (347). This research suggests that the disease

prevalence identified by HepFree cannot be used to predict prevalence in other migrant populations residing in England. Research by Hellanius et al however identified that individuals with risk factors for poor health were more likely to engage in screening performed opportunistically (348). Therefore in HepFree, although the population recruited as a result of letter invitation may have represented a healthier cohort, perhaps this was counteracted by the opportunistic testing element of the trial.

8.3 Comparisons with other studies.

8.3.1 Prevalence

Performing research to establish the prevalence of viral hepatitis in immigrant populations is not a new concept. Multiple previous case-finding studies have been performed, but vary in several aspects including the demographics of the cohorts studied, the duration of the trial, the methods used to invite eligible participants and the locations used for testing, the methods used to consent and to test participants, and finally the viruses tested for (300-304,331,332,343,344,349,350). In this section I will discuss in detail the outcomes of the HepFree trial and compare our results with data from previous trials.

As discussed in the introduction of this thesis, establishing the true prevalence of anti-HCV and HBsAg in any country is difficult, primarily due to the asymptomatic nature of both of the diseases and the case-finding initiatives that are currently in operation. The prevalence of any disease varies both with time and the demographics of the individuals assessed. In England, multiple initiatives have been developed and implemented to estimate the prevalence of viral hepatitis in populations of people who inject drugs. As a result of this, prevalence data derived here will have been influenced by the rigorous testing practices in these sub-groups. In England, the overall prevalence of anti-HCV and HBsAg in adults have been estimated at 0.54% and 0.3% (1,2,351). In our trial of viral hepatitis prevalence in immigrant populations in Bradford, the prevalence of anti-HCV and HBsAg were 0.9% and 0.8% respectively.

HepFree data was further analysed to determine the rates of infection in individuals depending on country of origin. In first generation immigrants, the prevalence of anti-HCV and HBsAg was 1.2% and 1.1% compared to 0.32% and 0.27% in second generation immigrants. A previous community based study conducted predominantly in first generation south Asian immigrants in Bradford observed a prevalence of anti-HCV and HBsAg of 1.4% and 1.6% respectively (301).

In order to determine why two case-finding studies conducted in the same area of England detected different rates of infection, trial design, locations selected, eligibility criteria and methods used to perform testing must be considered. There were significant variations in the demographics of the populations approached in the two trials. The target population for HepFree included all immigrants registered at a GPs performing targeted testing that had

either originated from, or who had a parent that had originated from a country with a prevalence of HBV of more than 2%. In the study by Uddin et al, testing for viral hepatitis was offered exclusively to individuals of south Asian ethnicity (301). The results of our trial demonstrated that individuals originating from countries in Asia-Pacific were more likely to be infected with anti-HCV; therefore concentrating testing solely in this ethnic group would potentially yield an increased number of positive results. In addition to differences in the ethnic origins of individuals invited for testing, unlike in the study by Uddin et al, the HepFree study population contained a large number of second generation immigrants. Although we have subdivided testing outcome data by generation, case-finding efforts in HepFree were not concentrated solely on first generation immigrants, therefore opportunities may have been missed to engage and test this group, in whom we know the rate of infection is higher.

The locations for testing in addition to the methods used to test for viral hepatitis also varied quite significantly between HepFree and the study by Uddin et al. In HepFree, testing was performed in GPs with blood taken by venepuncture and sent away for analysis in a laboratory. In contrast to this, in the study by Uddin et al, testing was performed in mosques and community centres, with oral fluid obtained for analysis.

In addition to the aforementioned differences, methods of recruitment varied significantly. In HepFree, individuals were sent an invitation letter to which they had to respond and book an appointment for the diagnostic test to be performed. In the study by Uddin et al, individuals were approached when attending either the mosque or a community centre; an appointment did not have to be made. As a result of this, it could be argued that in HepFree, recruitment and testing occurred in a more health conscious cohort because an individual had to elect to book an appointment to participate.

Finally, the study by Uddin et al was performed in the same geographical area as HepFree and this may have had a negative impact on prevalence data obtained in HepFree. The study by Uddin et al was performed in the same postcode districts as HepFree, therefore in addition to reducing the number of eligible participants for HepFree, the study by Uddin et al may have resulted in an increase in both the profile of, and awareness about viral hepatitis, which in turn may have led to an increase in subsequent ad-hoc testing in primary care after 2008 (301). This theory is supported in part by The Public Health England report into Hepatitis C in migrant populations. This report stated that sentinel surveillance data had identified an

increase in HCV testing between 2010-2014, and this increase in testing was attributed to targeted awareness-raising campaigns among Asian and British Asian communities (285).

HepFree trial results have once again demonstrated that the prevalence of both HBV and HCV in immigrants originating from outside the UK is higher than that in the indigenous population. This finding is consistent with, and supports results obtained from previous case-finding programmes performed in immigrant populations (300-304,331,343,340,349). Although data obtained from HepFree confirms that the prevalence of viral hepatitis is greater in ethnic minority groups, our data did not support findings from other studies performed in Western countries that suggested that the prevalence of disease in immigrant populations reflects their country of origin (349,352).

HepFree data on the prevalence of viral hepatitis in second generation immigrants are especially valuable as this is the first time that widespread targeted testing has been performed in this cohort of individuals. Results from the tests performed as part of HepFree have demonstrated that the prevalence of disease in this cohort is low, and in fact reflects the country of origin of the individuals tested. These findings are consistent with, and support findings from smaller studies that have speculated that infection in immigrants is acquired prior to arrival in the UK and that future screening efforts should be focussed on first generation immigrants (301).

In HepFree, in the cohort that attended for testing, a higher prevalence of chronic HBV was detected in males compared to females. Historically, in cases of acute hepatitis B, the difference in infection rates observed between genders has been attributed to high risk sexual activity in both homosexual and heterosexual males. Interestingly however, the same trends in prevalence have been observed in studies concentrating on migrant populations where the predominant modes of infection are presumed to either be vertical, or horizontal, during the first few years of life (353,354,355).

No clear explanations have been proffered as to why these differences in prevalence rates between genders occur. Although no studies have been conducted that explain why females appear to clear the virus more efficiently, associations have been made between the role of hormones and HBV related complications. In a case-control study performed in Shanghai, a

relationship was identified between high serum levels of testosterone and the development of HCC (356).

In HepFree, 25 cases of RNA positive chronic HCV were identified. There was evidence of previous infection associated with spontaneous viral clearance in a further 25 participants. In the HepFree cohort, disregarding participants that attended for testing despite having already received antiviral-therapy, spontaneous eradication occurred in 50% of cases with a positive test for HCV indicating previous exposure to the virus. HCV clearance rates observed here are higher than what has previously been reported in a systematic review of longitudinal HCV studies. In this review, spontaneous clearance of HCV occurred in approximately 25% of cases of infection (357). The rate of spontaneous clearance observed in HepFree also differed from that observed in the study by Uddin et al, where the rate of chronic infection in predominantly genotype 3 infected individuals was 96%. The authors of this study speculated that the genotype of infection may have been responsible for the low rate of spontaneous clearance observed, however this is not supported by either the findings of HepFree or a study by Lehmann et al (358). Although we are not able to scientifically prove the genotype responsible for infection in individuals no longer infected with HCV, taking into account the demographics of the anti-HCV positive RNA negative participants, the favourable genotype responsible would also have been 3.

8.3.2 Recruitment

In the section titled Review of results, comparisons were made between testing rates observed in the HepFree trial with both pre-existing preventative screening programmes in England and previous viral hepatitis case-finding studies that have been performed both in England and overseas. In this section, further comparisons will be made including the methods of recruitment used in order to gain information on both the acceptability of targeted testing as well as the superior method of invitation.

With the exception of one pilot study in London, that was terminated prematurely due to poor response rate, HepFree was the first viral hepatitis case-finding trial to target immigrant populations using a combination of methods including both letter invitation and opportunistic recruitment strategies (344). It was not however the first viral hepatitis prevalence study to use letters to invite the target population (331). In HepFree, more than 80% of individuals

were recruited either on the same day that the letter was generated by the GP practice or after thirty one days, suggesting that recruitment in these cases was opportunistic.

Previous literature studying response rates to invitation letters in preventative screening strategies has suggested that response rates are influenced by a multitude of factors including the ethnicity and socio-economic status of the recipient in addition to the condition being screened for (306-308,310). Research into pre-existing preventative screening programmes have reported conflicting results with regards the effectiveness of letter invitation in engaging ethnic minority groups. A plethora of evidence exists that suggests participation in pre-existing preventative screening programmes that use letter invitation including cervical, breast and colon cancer is lower in ethnic minority groups (308-310). These findings however were not supported in a study investigating attendance by ethnic minority groups at cardiovascular screening in primary care. In this cross-sectional study by Dalton et al, an increased response to letter invitation was observed in individuals of south Asian and mixed ethnicity compared to white individuals (359). The differences in findings observed may therefore not be related to the method of invitation but the condition being tested for.

Given that there are both time and financial implications associated with creating, generating and distributing letters to invite individuals to participate in preventative screening programmes, although we do not feel the results of our study are rigorous enough the claim that letter invitation is not effective, we feel that further research is required to directly assess the impact of letter invitation on engagement, especially in viral hepatitis testing. The results in this thesis do however suggest that including information relating to the disease that is being tested for at the time of the invitation is beneficial.

In HepFree, the combination of recruitment methods resulted in an uptake rate of 35.7%. As discussed previously, this was higher than in other 'opt-in' viral hepatitis testing programmes that have been performed but lower than what has been observed in both antenatal HBV and HCV screening trials (303,304,331,343,344). In this section I will discuss factors that may be responsible for the above findings, including the duration of testing in each trial, the populations targeted for testing, the locations where testing was conducted and the methods used to consent individuals.

Participation rates exceeded 70% in case-finding projects performed in antenatal settings in England and Hungary (343,344). To note, in the trial by Ward et al, testing was not offered exclusively to migrant populations, but to all women that attended for antenatal care where the trial was being conducted (343). As discussed previously, the populations studied in these trials vary significantly from the HepFree trial population; they were homogeneous, both in terms of age and gender. We speculated that trial participation in an antenatal setting may have been influenced by both convenience sampling as well as the psychological effect of a possible diagnosis of viral hepatitis.

Significant variations were identified between the methods used to obtain consent for testing between the antenatal trials and HepFree, making it difficult to draw direct comparisons between trial outcomes. In the trial by Ward et al, verbal consent was taken as opposed to written consent. A review of approaches used to improve participation of culturally and linguistically diverse populations in clinical trials identified that written consent acted as a barrier preventing participation in research (360). A perceived loss of confidentiality, loss of an individual's right to withdraw or object to treatment, and a lack of understanding of complex terms featured within the consent form were all identified as barriers preventing participation in studies that require written consent as part of the recruitment process (313).

In addition to the written consent process, multiple other factors have been identified that might have impacted on HepFree recruitment. Within the practices, loss of motivation by staff to offer and promote testing due to the relatively long duration of the trial, reduced availability of staff to perform administrative tasks including generating invitation letters and the potential time implications for staff in performing opportunistic testing could have all impacted on HepFree recruitment rates.

Time restraints and a lack of both resources and support have previously been identified as factors preventing effective research from being conducted in a primary care setting (361). In England, there has been an increase in the workload experienced in general practice. Work commissioned by the Royal College of General Practitioners (RCGP) identified that the number of GP consultations in England had risen from 303 million in 2008/09 to 361 million in 2013/14, an increase of 19% (362). In addition to enduring an increase in service use, over the past ten years an emphasis has been placed on regulatory requirements in primary care including QOF, enhanced services, revalidation and appraisal. The increased work load has

not been reflected in resource allocation; the share of NHS expenditure given to GP fell from 10.3% in 2004/5 to 8.4% in 2011/12 (362).

As well as practice related barriers, participant factors including difficulty in attending the surgery for an appointment due to work or family commitments, difficulty in arranging an appointment due to a lack of familiarity with how services operate or a language barrier, and the perceived implications of signing a consent form may have all impacted on trial recruitment.

As discussed previously, in HepFree, testing occurred more frequently in females compared to males. In addition to the reasons that have already been identified and discussed, the differences in recruitment rates may have occurred because of factors that prevent men from attending appointments in primary care. A report into the state of men's health in the European Union in 2011 recognised that men are more than twice as likely to work compared to women. This may result in difficulties in organising an appointment, when taking into account both working hours and surgery opening times (363). In addition to this, migrants are often employed in low skilled work associated with long and unsociable hours and may not be aware of their employee rights to seek time off to attend medical appointments (364). The European Commissioning report also identified that men are less likely to know how to book an appointment with a doctor, again resulting in decreased attendance (363).

8.4 Strengths and weaknesses of the HepFree trial

8.4.1 Trial location and participant searches

All prevalence studies are hampered to different degrees by multiple sources of bias. In this section I will discuss potential sources of bias arising from the methodology used in the HepFree study. HepFree was based in primary care, with the target populations identified from pre-existing demographic data stored in electronic medical records on clinical computer systems within each practice. The inclusion criteria for the trial were broad, allowing us to target a wide and varied cross-section of the community and the trial aimed to invite all individuals that fulfilled the inclusion criteria at each practice that had been randomised to the intervention arms of the trial.

One potential source of bias in HepFree relates to the locations selected to perform the trial. In HepFree the location for testing was the GP surgery, with trial related tasks performed by allied healthcare professionals that were permanently employed there. By conducting testing at each GP practice that was recruited to run HepFree, we were able to ensure that all eligible individuals that were invited to participate lived within a certain distance of a testing location.

In Bradford, all GPs operate using an appointments based system, with walk-in appointments primarily reserved for individuals who are acutely unwell. The use of appointments for testing may have had a negative impact on trial participation if participants were either unable to obtain an appointment to attend, or were unaware of how to make an appointment at their surgery. This may be particularly relevant in cases of individuals who are either self-employed, or those who work on a shift pattern.

Other disadvantages that have been identified associated with using GPs mainly relate to the methods used to identify the study population. As discussed in Materials and Methods, searches were created by the trial team to identify the potential study participant population from the clinical computer systems in the GP surgeries. The searches identified individuals based on demographic data that already existed in their primary care electronic medical record. However, deficiencies have previously been identified in the recording of diversity data in primary care (365). This would have a negative impact on participant identification in HepFree because missing demographic data would result in the eligibility searches omitting to identify all individuals registered at the practice that would have been eligible to participate in

testing. An alternative method that could have been considered for use to identify ethnic minority groups for research would have been name recognition software such as Onomap and Nam Penchan (366,367). These alternative methods however are not without their own limitations. Previous studies have identified that name recognition software packages often produce large numbers of false positive results and this, in turn would impact on the validity of the prevalence data obtained (366,367). In addition to this, these software programmes fail to take into account ethnic mixing; individuals that have changed surname, including those who have married into another ethnic group and their offspring.

Finally, through basing targeted testing for viral hepatitis in primary care and identifying the target population for the study using clinical computer systems, the HepFree trial has failed to address the prevalence and associated burden of disease in a large cohort of migrants that are not registered with a GP. This group of individuals, likely to consist of irregular and undocumented migrants may have either been illegally trafficked to the UK or failed to leave the UK once their asylum claims had been refused.

8.4.2 Methods of recruitment

In the original protocol for the HepFree trial, participants were invited to participate using a letter invitation that was generated and distributed by staff in each GP surgery. The protocol was subsequently amended to enable participants to be recruited via an opportunistic approach. In this section I will discuss both the letter and opportunistic methodologies used.

The intention of the trial was to send all potential study participants an invitation letter and a patient information leaflet about the trial to the home address documented on their medical record. These documents were sent both in English and in the individual's native language if this was known and a translation of the documents was available. The use of translated documents was employed to reduce any selection bias that might have arisen as a result of a language barrier.

As part of the trial design, it was the responsibility of the administrative staff within the GP practice to personalise, generate, and distribute the invitation letters to their own eligible study population. The trial was designed in this way for two reasons. Firstly, if targeted

testing for viral hepatitis in immigrant populations was found to be cost effective, and screening therefore recommended, the trial had to prove that the methods used could be replicated by all GPs in England. Secondly, findings from previous research that has investigated the effectiveness of invitation letters in engaging participants in health promotion suggested that individuals were more likely to respond to invitation letters generated by the primary health care team responsible for providing care, compared to 'mass mailing' campaigns from a screening programme (368). This finding was supported by a Cochrane review in which analysis of personalised GP invitation letter versus invitation letter from other authority sources demonstrated that uptake of screening was higher in the GP cohort compared to those receiving letters from programme coordinators (369).

One clear disadvantage of using practice staff to generate and dispatch the letters was that the research team could not control the volume or frequency that the letters were sent. As a result of this, some potential study participants did not receive an invitation to participate in HepFree and this will have inevitably impacted negatively on trial recruitment data. An alternative and arguably more efficient method of producing the invitations that would have also enabled the trial team to control the number sent each month would have been to outsource this task to a professional printing company. This would have improved trial efficiency, ensuring that participants received their invitation in a timely manner to enable them to attend for testing, but would have prevented us from being able to assess how practices coped with the additional administrative work load associated with testing large groups of individuals for viral hepatitis. This may not have mattered however because from discussions with clinicians it became evident that it is quite rare for administrative tasks such as 'mass mailing' invites for example for influenza vaccinations to be performed in the practice, now, most practices outsource this task to save time and reduce the administrative burden on practice staff.

Following the introduction of opportunistic recruitment and testing, an improvement was seen in uptake of the trial. The opportunistic recruitment methodology also helped to reduced bias arising as a result of any of the following: an individual not receiving the invitation letter, not been able to read or understand the content of the letter and finally any stigma associated with been invited to attend for viral hepatitis testing via written invitation. Recruitment to HepFree was not changed solely to opportunistic methods though as this would have created bias from convenience sampling, with participants only included in the trial if they attended the GP for another reason, thereby potentially resulting in a study population comprised of individuals with an increased number of co-morbidities.

From trial data collected, it was evident that opportunistic recruitment and testing had been performed in some practices. There were significant variations observed in the numbers of participants consented and tested per practice though, suggesting that either some practices were more proactive than others in approaching potential study participants to take part in HepFree, or alternatively that recruitment had been influenced by selection bias. Bias may have arisen if staff only offered the hepatitis test to individuals that they perceived were at high risk of infection, or alternatively if they omitted to offer it to individuals where they felt the offer of testing might not be well received. Potential sources of bias arising from opportunistic recruitment and testing at a practice level could have been explored in more detail by creating a prompt that documented in the electronic medical record whether testing had been offered to an eligible participant in the practice and the outcome of the offer.

One further weakness identified relating to recruitment in HepFree is that the trial collected very little information on participants that declined the offer of participating in the trial. We did not have permission to collect any additional information other than aggregate data on the number of participants that declined viral hepatitis testing per practice. It is also important to recognise that the group that formally declined the offer of viral hepatitis testing and therefore had a Read code demonstrating this in their electronic record does not represent the entire cohort that were invited to attend for testing and failed to respond to either decline the offer or to participate. A sub-study linked to the HepFree trial has attempted to address attitudes towards testing for viral hepatitis and may help to establish why some individuals do not wish to engage with the project.

This qualitative sub-study, conducted through semi-structured telephone interviews, focused on individuals attitudes towards testing for viral hepatitis. It was conducted in two practices in Bradford, prior to targeted testing commencing through HepFree. In the two practices, 1000 potential study participants were approached and asked to participate in this interview that assessed an individual's knowledge, views and attitudes towards viral hepatitis. Once the interviews had been completed the practice could begin inviting their eligible populations for testing. The data collected will be interpreted alongside recruitment data once all practices have completed the eighteen months of recruitment and testing to increase our understanding of potential barriers to widespread screening in immigrant populations.

8.4.3 Sample collection and interpretation

In HepFree, venepuncture and blood draw was performed to test individuals for viral hepatitis, with samples sent for serologic testing. Study samples were sent with a study specific proforma to a single laboratory for analysis. The purpose of the study specific proforma was to alert laboratory staff in the laboratory that the sample received for testing was part of the HepFree trial. This helped in the event of a problem arising with a study sample as the laboratory were aware of a named person for the trial to contact (the research fellow, myself). In addition to this, from a safety point of view, by using the bespoke proforma, laboratory staff were aware that the sample was a potential infection risk and to ensure that appropriate precautions were exercised.

In the laboratory, each sample was tested for anti-HCV using third generation enzyme immunoassays and for HBsAg with enzyme linked immunosorbant assays. These are the gold standards for testing with reported diagnostic sensitivity and specificity in excess of 99% (129,131). All samples confirmed anti-HCV positive were automatically referred for PCR testing to establish chronic infection status. Samples that tested positive for HBsAg were further analysed to obtain e-antigen and e-antibody status.

Several disadvantages were identified with regards to the methods of testing selected for HepFree. From a participant point of view, venepuncture can be uncomfortable and may act as a barrier to participation, especially in cases of needle phobia. Secondly, if venepuncture was unsuccessful, a participant would need to have a repeat procedure either on the same day or at a subsequent visit and this may result in loss of follow up. Thirdly, sending samples for serology incurs a time delay in reporting of results of at least 24 hours. This delay might act as a source of anxiety from a participant perspective.

Alternative methods for BBV testing are available, including point of care tests (POCTs) and dry blood spot (DBS) testing. The major advantages of POCTs are that they can be performed in the community without the need for either skilled technical staff or laboratory equipment in the first instance. The tests can be performed on a variety of body fluids including oral fluid, thereby offering a non-invasive and potentially more acceptable method of testing from a participant point of view. The results of POCTs are usually available within 5-30 minutes, allowing the study participant to be informed of their results during the same visit. In addition to reducing any potential anxiety associated with a delay of results reporting, it

would provide staff with the opportunity to counsel participants with a positive result face to face and discuss follow-up. This may help to improve subsequent engagement with assessment and treatment (370).

There are however several disadvantages associated with POCTs. Although some assays, for example oraQUICK provide results with the same high levels of sensitivity and specificity as immunoassays in a laboratory, for other brands, diagnostic accuracy for detection of anti-HCV is reduced, ranging from between 79-92%, (370,371). In addition to this, although POCTs have been designed for use on bodily fluids other than blood, reduced diagnostic sensitivity has been observed when tests have been performed on oral samples (371). In addition to this, unlike POCTs that are available for HIV testing, that quantify viral load in addition to confirming a reactive test, in the event of a positive HCV result, an individual would still require a further blood test for confirmatory PCR testing.

In HBV, previous studies have produced conflicting results with regards to the diagnostic sensitivity of POCTs. A systematic review and meta-analysis of diagnostic data has demonstrated high pooled accuracy for POCTs in the detection of HBsAg, however the diagnostic sensitivity of individual tests varies between 43.5% to 99.8% (372).A reduction in the diagnostic accuracy of POCTs in cases of HBV with a low viral load; usually termed the inactive carrier phase of HBV infection have been identified and this reduction in diagnostic accuracy could result in under-detection of new cases of chronic HBV infection (373,374).

Other factors that need to be taken into account when considering the use of POCTs for viral hepatitis testing in primary care are the attitudes of the clinicians responsible for interpreting the results, the attitudes of the healthcare professionals performing the tests and the attitudes of individuals being offered the test. A large amount of literature exists relating to the use of POCTs in screening trials for HIV. One study that investigated the feasibility and acceptability of performing HIV screening using POCTs in GUM clinics and community outreach centres demonstrated that both service providers and clients were accepting of this form of testing. Here, more than 90% of clients included in the study stated that they would recommend this method of testing to other people. The authors of the study did recognise some of the potential limitations of their study findings. In this trial, the target population consisted of a large proportion of homosexual men, a cohort of individuals that are usually both vocal and well informed regarding matters related to HIV including testing, diagnosis and access to treatment (375). This group therefore does differ quite significantly from the target

population of HepFree. In our population, previous studies have demonstrated a poor level of knowledge and understanding of viral hepatitis including the implications of a positive result, therefore receiving the diagnosis on the same day that the test is performed may be overwhelming.

With regards to the attitudes of clinicians and healthcare professionals performing the tests, a qualitative study exploring the use of POCTs in primary care identified concerns from respondents relating to the accuracy of results obtained from POCTs. This lack of trust in the diagnostic accuracy of tests may result in clinicians either reducing the number of tests being performed or being reluctant to counsel a patient on a positive result derived from a POCT prior to another method of testing being performed to provide confirmation (376).

A large cluster randomised control trial performed in primary care in Hackney, London investigated the impact of 'opt-out' rapid tests on the diagnosis of HIV in adults newly registering at practices. Here, the GPs were randomised to either perform the intervention or continue standard care. Trial adoption by GPs was good; 89% of practices approached were included in the trial. In the twenty intervention practices 11, 180 tests were offered and 4,978 participants accepted a test, corresponding to an uptake rate of 44.5% (377). Significant variations occurred in testing performance between practices and this was reviewed by the authors in an attempt to establish what factors impacted on screening activity (329). In this follow-up study, interviews were held with members of staff that had participated in the trial. A lack of clinician support for the allied healthcare worker performing the test was identified to have a negative impact on recruitment. A key theme evident from the interviews was that although the task of performing the rapid test was easy, the potential of diagnosing a stigmatising and potentially life-changing illness made staff more wary of the process, especially if a test performed was reactive, indicating active infection. Interestingly, although the individuals performing the test reported concerns about the prospect of a test being reactive indicating the presence of disease, this event had a positive impact on subsequent testing activity. In HepFree because each study sample was sent for laboratory analysis and the result sent back to the lead clinician, feedback of positive results to the healthcare workers performing the screening may not have occurred and therefore we are unlikely to have observed this effect in our case-finding trial.

Dry blood spot (DBS) offers another alternative method of testing for BBVs. Similar to POCTs, venepuncture is not required; laboratory processing of samples is still required though,

incurring a delay in the reporting of sample results. In addition to this delay, not all laboratories in the UK currently offer DBS analysis. Similar to POCTs, a reduction in diagnostic sensitivity has been identified in cases of HBV with low viral load (378). Furthermore, although DBS testing can be used with confidence to diagnose chronic infection with HCV, a systematic review has suggested that it is less accurate in its ability to quantify viral load. Contemporary treatments for HCV however do not require pre-treatment viral load quantification in order to determine the duration of therapy, so this is probably of less clinical importance than previously (379).

8.4.4 Reporting of results

One of the mandatory requirements specified in the trial protocol was that Read codes were entered in the electronic medical record of each participant undergoing testing to document the results of the tests performed. The reasons for this were to firstly ensure that the results of all study blood tests were reviewed, thereby reducing the chances that positive tests were missed, but also it enabled the trial team to produce anonymised reports from each HepFree practice containing the following data: the date that the hepatitis test performed, the results of the test and demographic data for each individual consented. The Read codes were provided to each practice by the trial team and a suggestion was made that ideally the lead clinician, but alternatively a member of the administrative staff took responsibility for inputting the Read codes. As well as the lead clinician within each practice receiving a copy of the blood test results, the PI in Bradford was also sent a copy of each set of results directly from the laboratory.

8.4.5 Generalisability of trial findings

In Bradford, a large number of individuals attended for testing, and the study population included a wide and varied mix of both first and second generation immigrants of different ages, genders and ethnic groups. The characteristics of the study population in addition to the trial setting and inclusion criteria helped to increase the generalisability of the trial findings. The only concern regarding generalisability arises around the number of participants recruited to the study. Less than 40% of eligible and invited participants were recruited and

therefore it may be difficult to use prevalence data from this cohort to draw conclusions about the prevalence of disease in all immigrants residing in Bradford.

One of the primary aims of the trial was to assess the feasibility of performing viral hepatitis screening in primary care. In order to investigate this, the trial team did not intervene or assist with either the invitation, or testing of eligible individuals. Through allowing the practices to conduct the study independently, data obtained can be used to draw conclusions about the suitability of the location selected for testing, as well as the methods used to both identify and invite potential study participants to establish whether this trial would be able to be replicated in the future.

In terms of establishing the acceptability of screening for viral hepatitis, we have to be aware that by conducting the trial in Bradford, we were performing a targeted testing project in both an area of England with a large immigrant population, as well as in a community with a large degree of ethnic diversity. It is possible therefore that the attitudes observed regarding acceptability of both offering and performing testing by staff in GP practices, as well as the attitudes towards testing observed from participants may differ in areas of England with smaller numbers of migrant residents.

8.4.6 Validity of trial findings

HepFree was a cluster randomised trial. The use of cluster trials in health-services research is increasing because this type of trial design is a well-recognised and pragmatic way of measuring the effectiveness of an intervention in this setting. The major disadvantage of cluster trials is that participants within a cluster are more likely to respond in a similar manner to one another and therefore cannot be assumed to act independently (380). Within HepFree, the effect of clustering was minimised by blinding all participants to the treatment location allocation of their GP practice until the point of the diagnostic assessment in secondary care.

8.4.7 Blinding

As discussed above, in order to reduce recruitment bias, all participants undergoing testing through HepFree were blinded to the assignment of their practice with regards to where treatment would take place in the event of a positive test result. For all participants that required follow- up for a positive hepatitis test, second stage consent was sought at the time of the diagnostic assessment in secondary care. Following consent, if a participant decided to remain in the trial, they were un-blinded to their treatment location allocation; standard of care versus community care.

8.4.8 Sample size

Both the number of GP practices and participants within each cluster reduced the risk of random error rendering the results invalid.

8.4.9 Statistical analysis.

In this preliminary analysis of data from one of the four sites in the UK conducting the HepFree trial, the effect of clustering was not taken into account.

8.5 Summary

This is the first viral hepatitis case-finding trial in England to effectively utilise electronic medical records in primary care to identify, approach and test immigrant populations that have been highlighted as 'at-risk' of viral hepatitis because of their demographic characteristics. Through the trial, we identified a high number of newly diagnosed cases of both chronic HBV and HCV.

HepFree is not the first case-finding study to identify a higher prevalence of viral hepatitis among immigrant populations. Despite this, to date, no formal recommendations for testing in this sub-group have been produced for widespread use. In the absence of guidance,

identification of cases of viral hepatitis in this population often occurs late, with majority of cases diagnosed with concurrent chronic liver disease (381,382).

Recruitment figures obtained from HepFree in Bradford suggest that immigrant populations find testing for viral hepatitis acceptable, however the methods used to engage this population may require some modification. As discussed before, we do not feel that the results of this analysis alone are strong enough to claim that letter invitation for future screening (if recommended) in this group of individuals is ineffective. In HepFree, the median number of days between an invitation letter been distributed and consent sought for testing was 51, increasing the likelihood that testing occurred as a result of an opportunistic approach of recruitment. Data collected does not however provide any insight into whether the letter impacted on an individual's decision to consent for testing when it was subsequently offered.

In HepFree, the number of participants that formally declined the offer of testing through HepFree was low, however the proportion of eligible participants that received an invitation letter and did not respond was high; 59.1%. These results suggest that when potential study participants were offered the test using an opportunistic approach, they were not averse to testing. The reasons for this might be that when offered a hepatitis test face to face, the timing was convenient and did not require personal motivation on the part of the individual to arrange an appointment for testing to be performed. With the exception of screening studies performed in antenatal women, the response rate to attend for testing in HepFree was comparable to other viral hepatitis case-finding studies.

Future research in this population is still required to address the methods used to engage 'difficult to reach' immigrant population. One possible method by which this could be done would be to assess the impact of performing case-finding for viral hepatitis in the same population but in several locations inside and outside of the healthcare setting at the same time. A trial combining both 'opt-in' and 'opt-out' testing in a variety of locations including primary, secondary and tertiary care centres in addition to in the workplace and at religious gatherings could result in greater access to and engagement of 'high-risk' individuals. A further strategy that could be considered to reduce the number of new migrants entering the country with undiagnosed chronic viral hepatitis would be for testing to be performed on arrival to the UK, possibly at the same time as tuberculosis testing.

8.6 HepFree sub-study discussion

8.6.1 Introduction

The HepFree sub-study was designed to investigate the impact of undiagnosed chronic HCV on healthcare utilisation in primary care. This retrospective, observational case-control study was designed, developed and run solely by the clinical trial fellow (myself) in Bradford with funding provided from the main HepFree trial. I designed the sub-study, wrote the protocol and completed the IRAS form in addition to submitting the study documents to ethics for approval. Once all permissions were in place, participant identification and data collection began in all practices that had been inducted and were actively recruiting participants for the HepFree trial in Bradford. In this chapter I will briefly present the sub-study and discuss the results obtained.

The sub-study had three broad aims, firstly to investigate whether individuals with PCR positive chronic HCV had an increased number of attendances to primary care compared to age and sex matched healthy controls. The definition of a healthy control was no evidence of current or past infection with either HBV or HCV. The second aim was to establish whether individuals with evidence of previous infection with HCV, defined by the presence of anti-HCV, but negative RNA, had a greater number of episodes of attendance to primary care compared to age and sex matched healthy controls. Through studying these cohorts of individuals we hoped to ascertain whether either current or past infection with HCV impacts on attendance frequency. Finally through analysis of the symptoms that prompted individuals with chronic HCV to present to their healthcare provider we aimed to identify key symptoms associated with the virus.

Through obtaining a better understanding of the potential burden of disease associated with HCV we may be able to strengthen the justification for widespread screening in high-risk populations. Currently, due to a combination of factors including both the cost of new DAAs as well as the workforce required for treatment of infected individuals, EASL recommends prioritisation of individuals for treatment based on strict criteria. EASL criteria currently recommend treatment in individuals with evidence of any the following: METAVIR fibrosis

score F3-F4, risk factors for progression towards more advanced disease, the presence of extra-hepatic manifestations of HCV infection and individuals at risk of HCV transmission. This group includes active injecting drug users, men who have sex with men engaging in high-risk sexual practices, haemodialysis patients and incarcerated individuals (299).

In contrast, there are very few recommendations for the timing of treatment in individuals with minimal or no fibrosis in the absence of extra-hepatic manifestations.

If the results of this sub-study identify that, irrespective of fibrosis score, individuals with HCV experience symptoms that in turn result in both a reduction in QOL and an increase in utilisation of primary care resources, then treatment of the virus in this cohort may ultimately be supported as the more cost-effective option.

The major strength of this sub-study was the population included in the analysis. The HepFree trial invited individuals for viral hepatitis testing based on their demographics, and therefore were presumed to be asymptomatic. We had permission to access the electronic medical records of individuals that were included in the sub-study in order to review attendances to primary care prior to testing and explore symptoms experienced without introducing bias. The major weakness of the sub-study was the relatively small sample size included in the analysis.

8.6.2 Review of the sub-study results

In Bradford, the only centre conducting the sub-study, 108 cases were included in the sub-study; 54 individuals with evidence of active or previous infection with HCV, 31 cases of RNA positive HCV and 23 cases with evidence of previous HCV; anti-HCV positive, RNA negative. The cases were matched to healthy controls using a ratio of 1:1. Within the sample there was a preponderance of female participants, 67% versus 33% respectively. The majority of individuals included in the sub-study were of Pakistani ethnicity, 88% versus 12% of individuals of other ethnicities. This finding was unsurprising as in the HepFree trial, when

expressed as a proportion of the total eligible population, testing occurred most frequently in individuals of Pakistani/British Pakistani origin.

The length of follow-up for individuals included in the sub-study was dependent on the length of time they had been resident in the UK and ranged from 1 to 12 years. Individuals with evidence of previous HCV infection and their matched healthy controls, labelled as groups 3 and 4 respectively, provided 210 and 208 patient-years of follow up. In comparison, the number of patient-years of follow up for participants with RNA positive chronic HCV and their matched healthy controls (groups 1 and 2) were 303 and 297 respectively. Per participant, the number of attendances was higher in groups 3 and 4, compared to groups 1 and 2.

Expected trends in the usage of GP services were observed in all age groups as well as for female participants compared to males. Year-on-year attendance was proportionally increased in each of the following: for the age groups 41-65 and 65 years and over, when compared to the baseline age group 18-40, for female participants compared to males, and for anti-HCV positive, RNA negative participants compared to healthy controls.

An analysis of the reasons for attendance identified that independent of gender and disease status, attendances for either a medical process or procedure was the most commonly coded reason for attending for an appointment. In males, 25.6% of all attendances and in females, 23.8% of all attendances were for this indication.

Attendances for problems relating to the musculoskeletal system were high in all cohorts. In group 1, presentation with a musculoskeletal complaint was the second most common reason for attendance in both males and females; 17.8% and 13.0% of attendances respectively. A higher number of attendances for problems relating to the musculoskeletal system were observed in the chronic HCV cohort compared to the healthy control cohort, 15.8% versus 12.1%, however this was not significant, $X^2 (1) = 1.13, p=.288$.

Attendances for pregnancy, child-birth and family planning were more frequently observed in cohorts 1 and 2, compared to 3 and 4; 4.8% of all attendances versus 2.7%. This finding is likely to be related to the differences in the mean ages of the individuals within the two sets of cohorts that were compared.

Attendances with a psychological theme occurred more frequently in the cohort containing healthy control participants compared to individuals with undiagnosed chronic HCV; 4.8% versus 2.5%.

8.6.3 Comparisons with other studies

At the time of inception, the HepFree sub-study was the first of its kind to retrospectively review the electronic medical records of individuals with a positive HCV test to explore both the frequency of attendances to primary care and the clinical indication prompting each attendance.

A plethora of studies have previously attempted to investigate the impact of chronic HCV on quality of life, with results obtained supporting the hypothesis that irrespective of either the mode of infection or the severity of disease, individuals with chronic HCV feel unwell and experience a reduction in QOL (196,204,205,206,207,213,383,384).

The impact of SVR on symptoms has also been explored (205,210–214). In these studies, eradication of the virus was associated with an improvement in symptoms. However, a large body of evidence with conflicting results exists. In these studies, the authors suggest that it is knowledge of the disease that impacts on both an individual's psychological and physical well-being (215,385-389).

As discussed previously, the HepFree sub-study compared primary care attendances in 54 participants with a diagnosis of either chronic HCV, or evidence of previous HCV with 54 healthy control participants. There was a preponderance of females in the cohorts with a positive HCV test, cohorts 1 and 3, 60% and 78% respectively. This finding is unsurprising and reflects overall testing activity in the main HepFree trial. In HepFree, a greater number of females attended and consented for testing compared to males and it was speculated that this discrepancy occurred because there were more opportunities available to perform opportunistic recruitment in females because of their increased use of primary care services. A report of trends in consultation rates in General Practice from 1995-2008 identified that apart from at extremes of age, females attended for a consultation more frequently than males. Reasons suggested for this observation included female perception of the state of their general health, attendances related to pregnancy, family planning and contraception and attendances with sick off-spring (334).

Research has suggested that perception of one's general health can vary depending on the ethnicity of the individual in question; therefore ethnicity may impact on primary care attendance rates. A report utilising census data to obtain information on limiting long-term illness demonstrated higher rates of illness reporting among Pakistani and Bangladeshi women compared to white women in 1991, 2001 and 2011. This same pattern of illness was not however observed in males of Pakistani or Bangladeshi origin (333).

In HepFree, the majority of men with a positive anti-HCV screening test were subsequently diagnosed with chronic HCV. 42% of participants in group 1 were male, compared to 22% in group 3. Age at the time of infection, ethnicity, immune status, gender and the presence of symptoms during the acute phase of infection have all been found to impact on the chances of spontaneous clearance of HCV (133,157-159,161,162,164). The role of gender in spontaneous clearance of HCV is debateable, with previous studies producing conflicting results. Two long-term follow up studies of female subjects infected with HCV from contaminated anti-D immune globulin reported spontaneous viral clearance in 45% of subjects (159,162). The rate of spontaneous clearance observed was higher than had previously been stated in the literature and did not support findings from larger population studies (133). The findings in the studies by Kenny-Walsh and Wiese et al may therefore be related to the homogeneity of the subjects included in the analyses. Their study populations consisted of young females, infected with HCV from contaminated anti-D during pregnancy, therefore it is likely that these participants shared very specific characteristics.

In the sub-study, the number of attendances per participant was higher for individuals in groups 3 and 4, compared to groups 1 and 2. This finding may be related to the differences in the ages of participants within the cohorts being compared. The mean age of participants in groups 3 and 4 was higher than in groups 1 and 2, 48 years versus 43 years. A report investigating trends in primary care consultation rates identified that the highest rates of attendance were observed in adults with advancing age (334).

In the sub-study sample, the mean cumulative visits per participant was higher in first generation participants originating from Pakistan compared to second generation participants of Pakistani origin, 58.2 versus 49.3. The relationship between migration and health status is complex, influenced by many factors including the process of migration, conditions in the host country, conditions in the country of origin, and the self-selecting nature of migrants. There is conflicting data available pertaining to the health of migrants. Some studies have suggested

that migrant groups have lower overall mortality compared to individuals indigenous to the host country despite lower socioeconomic status (390). Other studies however have suggested that this 'healthy migrant effect' diminishes with time, and the longer the duration of residence in the host country, the higher the rate of mortality in migrants (336,391). In the sub-study, attendance patterns observed in first and second generation immigrants were consistent with a systematic review of migrant utilisation of somatic healthcare services in Europe (392).

In participants with a positive HCV test that were included in this sub-study, attendance data prior to the episode of testing did not differ significantly when compared to age and sex matched healthy controls with no evidence of HBV or HCV. Our study findings therefore support historical research that suggests symptoms in the presence of HCV occur once the diagnosis has been made (215). The psychological impact of a diagnosis of HCV has previously been explored in several studies (215,385,387–389). Rodger et al identified that individuals with pre-existing knowledge of their disease status reported a significant reduction in multiple QOL scores. Individuals with pre-existing knowledge of their diagnosis reported greater limitations in their abilities to perform daily activities, as well as an increase in body pain, poor social functioning and emotional problems compared to population norms (215). Interestingly, in the cohort of individuals included in the study that were unaware of their HCV diagnosis, significantly lower QOL scores were reported in areas pertaining to general health, vitality and mental health compared to population norms, but subjects did not feel that either their emotional or physical health impacted on activities of daily living (215). The authors therefore proposed that the global reduction in QOL observed in the cohort aware of their infection may have occurred as a result of labelling (215).

A subsequent cross-sectional study performed to investigate psychological well-being, mental health and QOL in women diagnosed with iatrogenic HCV infection supported the findings of the study by Rodger et al (385). In this study, psychological well-being of two cohorts of individuals were explored; women with evidence of chronic HCV infection and those with previous evidence of HCV infection. The authors demonstrated a reduction in psychological well-being in both groups of women compared to healthy British women (385). The authors did not identify any relationship between the degree of hepatic inflammation and well-being of the subjects studied and inferred that the results obtained suggested that problems arising in subjects with HCV were related to the social impact of a diagnosis, misconceptions regarding the route of acquisition of the virus and embarrassment (385). The authors further speculated that embarrassment and stigma were strongly correlated with episodes of

depression and anxiety in the context of a positive diagnosis (385). Interestingly, in this study the potential psychological impact of HCV was also observed in the views and beliefs expressed by individuals declining to participate. Non-responders to the invitation to participate in the study used the following reasons; a desire not to think about their diagnosis and a reluctance to disclose their HCV status (385).

The impact of stigma in HCV infection was evident in a review of the health status of Irish individuals with iatrogenic HCV infection. In this review, illness related stigma was observed in 51% of participants surveyed (393). A more comprehensive investigation of the relationship between stigma and a broad range of measures of psychological wellbeing and adaptation to illness has also been performed in individuals with HCV (389). This study identified a high prevalence of psychological symptoms in individuals with HCV (389). The researchers identified that even after adjusting for age, gender, route of infection and social class, the risk of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) depressive disorders was increased in individuals that perceived HCV-related stigma. The authors identified a relationship between stigma and other aspects of adjustment to illness including higher frequency and perceived impact of symptoms and greater perceived impairment of thinking and concentration (389).

The results of the studies discussed above, in addition to findings in studies by Cordoba et al, have proposed that disease labelling is central to the adverse psychological profile of individuals with HCV and conclude that although there are studies that propose alternative mechanisms responsible for symptoms experienced by infected individuals, the evidence is not compelling (386,387).

The adverse psychological impact of a diagnosis of chronic disease is well recognised in other conditions, for example in inflammatory bowel disease, and favourable results in health outcomes have been observed following the implementation of strategies aimed at improving social support in individuals affected (394,395).

In our sub-study, for each participant, the clinical outcome of each attendance was coded using the Wonca Internation Classification Committee International Classification of Primary Care Second Edition (ICPC). In previous studies, musculoskeletal pain, fatigue and depression have been frequently reported by individuals with HCV (159,162,169,186–188,199,384). In the HepFree sub-study, attendances with a musculoskeletal problem were common in all cohorts, independent of disease status. This finding may be related to the ethnicity of subjects included the sub-study.

It is well recognised that musculoskeletal pain is more widespread among ethnic minority communities residing in the UK. In a study of Pakistani immigrants residing in England, there was an increased prevalence of musculoskeletal pain compared to individuals of the same ethnicity residing in Pakistan (396,397). In a review of musculoskeletal pain in ethnic minority groups of south Asian origin residing in England, authors concluded that there was a lot of support for an association between psychological distress and the reporting of symptoms of pain (398). Given that the majority of participants included in the sub-study were of south Asian origin, and data collection was performed retrospectively, it would be difficult, if it was not documented in the electronic record, to be able to differentiate between true musculoskeletal pain and somatisation.

It has been speculated that pain is a frequent presenting complaint in ethnic minority individuals because of cultural stigma surrounding mental illness. Focus groups conducted in south Asian communities in London demonstrated the ingrained acceptance of secrecy because of shame associated with mental illness (399). Our sub-study did not identify an increased prevalence of psychological disorders in individuals with HCV, with fewer attendances observed in the cohorts with a positive HCV test compared to healthy control subjects.

8.6.4 Strengths and weaknesses of the sub-study

8.6.4.1 Study design

The HepFree sub-study was a retrospective case control study, designed to investigate the impact of undiagnosed chronic HCV on primary care attendances. Information on episodes of care that had occurred prior to screening was obtained from journal entries in the electronic medical records stored on clinical computer systems in GPs. The major limitation with this method of data collection was that information on previous attendances stored within the medical records was not collected or recorded specifically for analysis in our sub-study and therefore there was variation in the quality of data available.

Read codes are a coded thesaurus of clinical terms that provide a standard vocabulary for use by clinicians to record patient findings and procedures in health and social care IT systems. In the medical records accessed for the sub-study, it was evident that Read codes are not used exclusively to document the outcomes of clinical encounters by clinicians and other allied healthcare professionals. This finding was supported in research that explored the feasibility of creating an ischaemic heart disease (IHD) register by searching for pre-existing Read codes in patient electronic records (400). In this study, authors concluded that from using Read codes alone, 31% of patients with IHD were not identified. Furthermore, 15% of patients that did have Read codes related to coronary heart disease within their notes had no evidence of the condition of interest clinically (400).

In the sub-study, collecting data pertaining to episodes of care that had been documented using Read codes was performed with ease. For consultations that were recorded using free text with no accompanying Read code diagnosis, we had to rely on the observations recorded by the clinician that had performed the consultation to establish the reason for attendance. Because data collection was performed retrospectively, we were unable to control which elements of each consultation were documented by the clinician. We have recognised that this could be problematic, especially in patients that attended primary care frequently for review, a group of patients often referred to as frequent attenders. Frequent attenders, as the name suggests, present frequently to primary care to seek medical opinions. At each consultation they often present several problems to the clinician, some of which may be psychosomatic in origin. It is the responsibility of the clinician to differentiate these from true pathology. This group of patients are therefore considered one of the most challenging to manage (401). Due to the high number of, and often unclear nature of problems arising in

these consultations, it is possible that not all aspects of each clinical encounter are documented. Therefore, in cases like this, it is possible that some clinical information that may have been useful and included in the sub-study for analysis would not have been documented and therefore would not be available.

8.6.4.2 Participant selection and recruitment

The sub-study was conducted using data collected from the electronic medical records of participants that had been recruited, consented, and undergone testing for viral hepatitis as part of the HepFree trial. Groups 1 and 3 of the sub-study consisted of individuals with a positive HCV test. Individuals in group 1 had subsequently tested positive for chronic HCV, whereas those in group 3 had a negative RNA test indicating spontaneous clearance of the virus. Groups 2 and 4 comprised of individuals that had consented to HepFree and had tested negative for both HBV and HCV. As described in Materials and Methods, control participants were matched to cases using the following criteria; gender, age, country of birth, ethnicity and length of time resident in the UK. Healthy controls that matched cases were selected from the eighteen GP practices that were performing targeted testing for HepFree. If more than one eligible control was identified using the criteria for matching listed above, a randomisation programme on Microsoft EXCEL was used to select the final control that would be included in the sub-study. The clinical fellow that performed participant selection was blinded to all clinical information about the control participant until they had been selected to prevent any bias from been introduced.

HepFree targeted and invited individuals to undergo testing for viral hepatitis based on demographic data stored in their electronic medical records. An assumption was therefore made that blood tests in HepFree were performed in asymptomatic cohorts of individuals, as opposed to viral hepatitis testing being performed in individuals that had either sought medical attention for investigation of symptoms, or alternatively in a cohort of individuals referred to a specialist hepatology unit. By performing testing in this general setting we had the unique opportunity to collect data retrospectively on attendances to primary care that had occurred prior to the trial intervention. This would hopefully enable us to establish whether individuals with undiagnosed chronic HCV accessed healthcare services more frequently than non-infected individuals prior to testing and diagnosis.

8.6.4.3 Data collection

In contrast to the majority of research performed to investigate symptoms in HCV, this sub-study collected data on episodes of care that had occurred prior to the diagnosis of HCV been made, by accessing individuals electronic medical records in primary care. By performing data collection in this way, we eliminated both recall and reporter bias as well as prevented the research findings from been influenced by the Hawthorne effect.

The methods used for data collection and recording were conducted in the same way for each participant enrolled into the sub-study. Prior to commencing data collection, variables that were going to be collected and recorded were agreed and documented by the research team. In order to minimise intra-rater variability, collection and coding of data relating to episodes of care for both cases and controls was performed by a single member of the research team (me).

One weakness identified relating to the method of data collection used relates to blinding. Ideally the member of the research team responsible for data collection would have been blinded to both the purpose of the sub-study and the research questions the investigators were attempting to address. Gearing et al stated that abstractors blinded to the hypothesis decrease reviewer bias, specifically the possibility of their assessment being swayed by knowledge of others, concern over adversely affecting the study outcome or interpreting their abstraction as too lenient or harsh (402). To reduce any bias that may have arisen secondary to the selection of participants to act as 'non-infected' controls, Microsoft EXCEL was used to select a control at random from the list of eligible and matched participants. It was only after the control had been selected, that the electronic medical record was fully accessed to collect data on episodes of care that had occurred prior to HepFree recruitment.

For the sub-study, information on episodes of care were collected either from the time the subject entered the UK and was registered with a GP or from 1st January 2005 for subjects that had moved permanently to the UK prior this date. For some participants, their first place of residence in the UK was not Bradford. In these cases we had to assume that GP2GP technology had transferred patient electronic medical records directly and securely between practices (403).We could not control for periods of time when participants that were included in the study visited overseas. It is common for immigrants to spend prolonged periods of time overseas either visiting or caring for family and during this time they may have accessed

healthcare services in the country they were visiting and we could not collect data on these visits. This same limitation however does also apply to all cohorts of participants included in the sub-study.

8.6.4.4 Generalisability of sub-study findings

The size of the sample included in the sub-study analysis was small; 54 cases with a positive anti-HCV test and 54 controls. In order to identify this number of cases, 8,973 individuals were enrolled and tested for viral hepatitis by the HepFree trial. There are several disadvantages with studies containing small numbers of participants, and these relate to the interpretation and significance of results obtained. In addition to there been difficulties in interpreting results obtained, false positive results can occur in studies with small sample sizes and it can be difficult to apply the results obtained from a study with a small sample size to the larger population.

8.7 Summary

Whether symptoms and a subsequent reduction in QOL in individuals with HCV arise as a direct consequence of the virus, or as a result of knowledge of the condition and the implications of long-term infection, failing to recognise and address these 'extra-hepatic' manifestations of chronic HCV can be distressing for patients. It is therefore essential that as part of the patient assessment, the degree and extent to which the diagnosis of HCV impacts on an individual's QOL should be explored and also be considered when timing of therapy is decided. In this sub-study, we did not identify an increase in healthcare utilisation by individuals infected with chronic HCV, however we do recognise that the sample size was small. Future research investigating the impact of targeted support and education implemented following a diagnosis of HCV on symptoms and health related quality of life may be beneficial in cohorts of infected individuals.

9. Summary

In this final chapter I aim to explore to what extent the objectives that were set out in this thesis have been achieved, contributions that have been made to the existing field of research by this piece of work and finally to provide some suggestions about the direction of future research in the same field.

Through reviewing the methodology and results obtained from both the HepFree trial and the sub-study on healthcare utilisation by individuals with undiagnosed HCV it is clear that although valuable in its contribution, modifications to the trial methodology will enable further advances to be made with regards to engaging high-risk immigrant populations in testing for viral hepatitis.

The broad aims of this thesis were to explore the feasibility of developing and running a future screening programme for viral hepatitis in immigrant populations based in primary care. The research questions we attempted to address were:

1. The feasibility of using electronic medical records held on clinical computer systems in primary care to identify the target population to be invited for screening.

2. The superior method of invitation to successfully engage the target population in screening.

3. The demography and prevalence of viral hepatitis in first and second generation immigrant populations residing in Bradford.

4. Whether undiagnosed chronic HCV results in greater use of healthcare resources in primary care.

In addition to this, by reviewing recruitment rates in each practice we hope to be able to comment on to what extent it is both feasible and acceptable to design a screening programme to be run independently by members of staff within GP.

Interrogation of primary care records to identify the target population to invite for screening

As described in chapters 1.0 and 8.0 at the time of inception, the trial team were not aware of any other active studies that were using demographic data that had already been collected and stored in electronic medical records in primary care to identify the target population to invite for viral hepatitis testing. The HepFree trial team designed a series of searches that, when published and activated on clinical computer systems in GP surgeries would identify individuals that fulfilled the trial inclusion criteria. The searches performed this task by identifying Read codes that had previously been recorded by clinical staff to document the country of birth, main spoken language and ethnicity of patients registered. These searches were referred to as eligibility searches.

The results of the eligibility searches, described in chapter 4.0, demonstrated that it was feasible to identify individuals based on demographic data that had been stored in Read code format in electronic records. The searches were designed to look for Read codes related to ethnicity as well as country of birth and main spoken language. Through these methods we aimed to reduce the number of individuals that would have fit the inclusion criteria but would not have been identified by the searches due to deficiencies in recording of demographic data. The results of our searches did identify on-going problems with the quality and completeness of demographic data recording in primary care. Although ethnicity recording was done very well; in excess of 90% of individuals registered in targeted testing practices had a Read code denoting ethnicity; country of birth and main spoken language were not completed to the same standard.

Although HepFree was the first viral hepatitis case-finding trial to identify its target population by using demographic data stored in primary care databases, it was not the first trial to utilise this method for potential trial participant identification. Read codes related to medical conditions have been used to identify a trial population in a study that aimed to develop an IHD register in primary care (400).

One of the major limitations in the HepFree methodology was that it failed to include an alternative method that would identify individuals that had no demographic data stored in Read code format within their record. Although HepFree demonstrated that electronic medical records store large volumes of information that can be interrogated by researchers, future research that utilises a similar method for subject identification could consider the

additional use of name recognition software to explore whether this increases the eligible population identified within practices. The one potential downside of this is method is that it would require a member of staff to manually confirm the results of the searches generated by these software programmes as they have previously been associated with large numbers of false positives (366,367).

The superior method of invitation used to engage the target population in screening

As discussed in chapters 1.0, 5.0 and 8.0, many challenges are faced when attempting to engage ethnic minority groups in screening programmes. These challenges arise for a multitude of reasons including low levels of knowledge pertaining to the condition being screened for, potential fear of stigma associated with a positive diagnosis, uncertainty surrounding the implications of infection and how the disease may affect either themselves or their family. Further obstacles acting as barriers to screening are related to language and literacy, uncertainty about how to organise an appointment to attend for screening, availability to attend due to work demands and participant willingness to engage both in screening and subsequent follow-up. In the context of a trial setting, additional fear surrounding the methods of consent has also been identified as a barrier to participation.

Previous research has identified that invitation letters endorsed by the clinician responsible for an individual's care improves engagement (345,456,368). HepFree therefore included the practice letterhead in addition to the lead clinician's signature on all invitation correspondence sent. In HepFree however, letters were not the sole method used to recruit potential study participants. In addition to sending the written invitation, individuals could be approached and tested opportunistically. Our results suggested that the type of invitation letter received did impact on an individual's decision to engage with testing through the trial. Nearly one third of individuals attended for testing within thirty-one days of the enhanced letter that also included an information sheet on viral hepatitis been sent, compared to only ten percent of individuals that received the standard invitation letter.

In the trial, in excess of eighty percent of participants that were recruited to HepFree consented for testing either on the same day that the letter was generated by the GP or after thirty-one days. We speculated that in these cases recruitment was opportunistic as opposed to the result of receiving the invitation letter. As discussed in chapter 5.0, although an assumption was created for the purpose of the analysis we do not feel that the results of the

HepFree study alone are strong enough to conclude that letters are ineffective as a form of invitation in ethnic minority groups. The HepFree trial demonstrated the effectiveness of a combination of different invitation approaches in engaging the target population.

Unfortunately due to stipulations in the trial protocol, we did not have the necessary permissions to be able to establish the extent to which opportunistic methods of recruitment impacted on an individual's decision to participate in HepFree. If future research was to be conducted in this area, a direct measure of the effectiveness of this approach would be useful in helping to decide whether screening programmes in the future should consider stopping inviting participants using letters as there are both financial and time implications associated with this method of recruitment. There would however be potential disadvantages to only screening individuals approached opportunistically in primary care. The most obvious disadvantage would be that the population included would represent a convenience sample. In addition to this, screening success would be solely dependent on members of staff within each practice adopting the trial and being motivated to offer screening.

Future research that aims to explore the impact of social media and health advertising campaigns on recruitment would be useful. In the 21st century there has been rapid expansion of the social media phenomenon with the proliferation of tools including Twitter and Facebook. Social medial has been identified as a both a platform enabling patients, families of patients and caregivers to share their experiences of diseases in addition to raising awareness of certain conditions (404). Therefore adapting the methods used to approach target populations may result in greater levels of engagement.

One interesting finding of the study was the extent to which different ethnic minority groups engaged with testing for viral hepatitis in Bradford. The demography of individuals recruited into the trial was described in chapter 5.0. Participation by individuals of Asian ethnicity was much higher than by other ethnic groups including white European and 'other ethnicity'. This may be the result of campaigns that have previously been launched within south Asian communities to increase the profile of viral hepatitis and encourage participation in screening. The use of focus groups to enhance our understanding of barriers that prevent participation in screening in these more difficult to reach ethnic groups, prior to adapting invitation methods may help to guide future research

The demography and prevalence of viral hepatitis in first and second generation immigrant populations residing in Bradford.

The HepFree trial design, with its broad inclusion criteria aimed to establish the prevalence of viral hepatitis in first and second generation immigrants residing permanently in Bradford. As discussed extensively in chapter 8.0 due to the relatively low response rate to the invitation for testing through HepFree, it is difficult to use the findings obtained from this study to make assumptions about the prevalence of disease in the larger immigrant population of Bradford.

The results of the trial were however very useful in providing information on the prevalence of disease in second generation immigrants in England. HepFree was the first viral hepatitis case-finding trial to engage a large number of second generation immigrants in viral hepatitis testing and the results supported those obtained from small studies that have previously been conducted. In 1,875 immigrants tested, the prevalence of anti-HCV and HBsAg were 0.32% and 0.27% respectively. These findings suggest that future formal screening efforts in ethnic minority groups should be concentrated in first generation immigrants as this is where the burden of disease is likely to be concentrated.

From our results, it was clear that higher rates of positive hepatitis tests were concentrated in non-English speaking immigrants, in individuals originating from countries within Asia pacific, in males, and in individuals of advancing age. In many ways the demographics of the high-risk group share similarities with those considered 'difficult to reach'. An analysis of recruitment outcomes in HepFree identified that it was more difficult to engage males in screening, and it is well recognised that language barriers act as an obstacle preventing individuals from accessing appropriate healthcare services.

In the trial, individuals with a positive viral hepatitis test result were invited to attend a diagnostic assessment carried out in secondary care that included investigations, both non-invasive and invasive on order to stage disease. Twenty percent of the trial population that were diagnosed with chronic HCV had evidence of advanced fibrosis/cirrhosis on staging investigations, indicating a significant burden of disease related to chronic HCV. In addition to the increased risks associated with treating these individuals with antiviral therapies, even after successful treatment they will require on-going surveillance for HCC and remain at an increased risk of both liver and non-liver related morbidity and mortality.

In the HBV cohort, fifteen percent of cases were found to have an elevated VL that would warrant on-going monitoring. In five percent of cases diagnosed with HBV, there were clear indications to commence antiviral therapy in order to try and reduce the incidence of liver related complications including HCC. Even in the small populations that were identified to have chronic viral hepatitis through HepFree, the significant burden of disease associated with viral hepatitis was evident and should strengthen the case for universal screening.

Whether undiagnosed chronic HCV results in greater use of healthcare resources in primary care.

The HepFree sub-study was designed to assess the impact of undiagnosed chronic HCV on utilisation of healthcare resources in primary care. It was unique in its design as it was the first time that primary care records had been reviewed retrospectively to establish both frequency of attendances as well as reasons for attendance in a group of individuals that were not aware of their infection status. Unfortunately, the major limitation of this sub-study was the small number of participants recruited. Despite performing testing in over 8,000 individuals, only 54 cases of previous or current infection with HCV were identified.

As discussed in chapter 8.0, previous studies that have attempted to investigate symptoms in individuals with chronic HCV have identified an increased prevalence of fatigue, musculoskeletal pain including arthralgia and myalgia as well as depression. The results of the sub-study failed to identify an increased prevalence of the above listed symptoms in the cohort with undiagnosed chronic viral hepatitis compared to the healthy comparison group. This finding may have occurred for several reasons. Firstly, it may be that the results of this sub-study support findings from other research that suggest symptoms occur in individuals with HCV as a result of knowledge of the disease as opposed to as a direct consequence of the virus itself. Alternative explanations for the results obtained may be that because in HepFree, disease was concentrated in non-English speakers, this group may have been more reluctant to engage with medical services even in the presence of symptoms because of the language barrier. Alternatively, because of the vague and often difficult-to-treat nature of symptoms that have previously been described in individuals with HCV, individuals may be reluctant to seek medical attention because they may perceive that it will not lead to any benefit in terms of improvement in symptoms. The small study population included in the HepFree sub-study means that all results obtained from data analysis need to be interpreted with great caution.

The feasibility and acceptability of performing targeted screening for viral hepatitis in primary care

One of the aims of the main HepFree trial was to establish whether performing targeted testing for viral hepatitis in high-risk groups in primary care to identify disease would be cost effective and therefore lead to future formal screening programmes being developed. At the time of writing this thesis, some GP sites were still open to recruitment, therefore data has not yet been analysed to address the question regarding cost effectiveness. If the outcomes of the trial suggest that it is indeed cost effective, then it is important to have established whether the location selected to host the screening programme is appropriate for widespread screening in the future.

In order to test this, although the trial in Bradford was overseen by a clinical fellow based in secondary care, after site recruitment and initiation, the practices were expected to perform the tasks of inviting and testing participants independently.

As discussed in chapter 3.0 considerable challenges were faced when attempting to recruit GP sites to perform testing for viral hepatitis through HepFree. The trial team encountered a myriad of logistical and contractual problems when trying to engage practices. In a large number of cases the primary reason given for declining the offer to participate in the trial was the perception that it would increase the work load within the practice. In England multiple screening trials are already conducted successfully in primary care and this is probably because although allied healthcare professionals within the practice perform the investigation, for which they are reimbursed, all other screening activities including inviting patients, processing test results and following up on results is performed by individuals outside of the practice. Therefore, the direct impact of these screening programmes on the work load of the practice is minimal. This was not the case with HepFree, therefore by modifying the methods to enable support to be provided both for administrative tasks including generating and distributing the invitation letters as well as support with processing and acting on results, engagement with testing for viral hepatitis by primary care clinicians may increase. Despite this, the results of the HepFree trial did suggest that once practices were engaged, they were willing to perform testing for viral hepatitis.

There was variation in recruitment between practices participating in HepFree. A non-significant positive correlation was identified between the number of potential study participants registered at a practice and recruitment performance. Future research exploring the reasons why discrepancies in testing performance were identified would be beneficial for future screening initiatives in a primary care setting.

In summary, the HepFree trial has been invaluable in investigating whether or not it would be feasible and acceptable to use GPs in primary care to both identify a population at high risk of viral hepatitis and then to perform screening in that eligible population. The results obtained from this initial analysis of the Bradford data further support that immigrants find testing for viral hepatitis acceptable; however adaptations both to the way that testing is offered and performed in this setting is required in order to increase participation.

References

References

1. World Health Organisation. Fact sheet: Hepatitis B [Internet]. 2016 [cited 2017 Jan 3]. Available from: http://www.who.int/mediacentre/factsheets/fs204/en

2. World Health Organisation. Fact sheet: Hepatitis C [Internet]. 2016 [cited 2017 Jan 3]. Available from: http://www.who.int/mediacentre/factsheets/fs164/en/

3. Health and Safety Executive. Hepatitis B Virus (HBV) [Internet]. 2015 [cited 2017 Jan 3]. Available from: http://www.hse.gov.uk/biosafety/blood-borne-viruses/hepatitis-b.htm

4. Health and Safety Executive. Hepatitis C virus (HCV) [Internet]. 2015 [cited 2017 Jan 3]. Available from: http://www.hse.gov.uk/biosafety/blood-borne-viruses/hepatitis-c.htm

5. United Nations Population Fund. Migration [Internet]. 2015 [cited 2017 Jan 3]. Available from: http://www.unfpa.org/migration

6. Office for National Statistics. Immigration patterns of non-UK born bopulations in England and Wales in 2011. 2013.

7. Shire A, Sandhu D, Kaiya J, Oseini A, Yang J, Chaiteerakij R, et al. Viral hepatitis among Somali immigrants in Minnesota: Association of hepatitis C with hepatocellular carcinoma. Mayo Clinic Proceedings. 2012;87(1):17–24.

8. Pollack H., Kwon S, Wang S, Wyatt L, Trinh-Shevrin C. Chronic hepatitis B and liver cancer risks among Asian immigrants in New York City: Results from a large, community-based screening, evaluation, and treatment program. Cancer Epidemiology, Biomarkers& Prevention. 2014;23(11):2229–39.

9. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. The New England Journal of Medicine. 2014;370(20):1889–98.

10. Kowdley K, Gordon S, Reddy K, Rossaro L, Bernstein D, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. The New England Journal of Medicine. 2014;370(20):1879–88.

11. Lawitz E, Poordad F, Brainard D, Hyland R, An D, Dvory-Sobol H, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. Hepatology. 2015;61(3):769–75.

12. Public Health England. Hepatitis C in the UK 2016 report [Internet]. London; 2016. Available from: https://www.gov.uk/government/...data/.../Hepatitis_C_in_the_UK_2016_report.pdf

13. Martin A, Lemon S. Hepatitis A virus: from discovery to vaccines. Hepatology. 2006;43(2 Suppl 1):S164-72.

14. Wise M, Sorvillo F. Hepatitis A-related mortality in California, 1989-2000: analysis of multiple cause-coded death data. American Journal of Public Health. 2005;95(5):900–5.

15. Nainan O, Xia G, Vaughan G, Margolis H. Diagnosis of Hepatitis A virus infection : a molecular approach. Clinical Microbiology Reviews. 2006;19(1):63–79.

16. Abbas Z, Afzal R. Life cycle and pathogenesis of hepatitis D virus : a review. World Journal of Hepatology. 2013;5(12):666–75.

17. Rizzetto M, Hoyer B, Canese M, Shih J, Purcell R, Gerin J. Delta agent: association of delta antigen with hepatitis B surface antigen and RNA in serum of delta-infected chimpanzees.Proceedings of the National Academy of Sciences of the United States of America. 1980;77(10):6124–8.

18. Bonino F, Hoyer B, Shih J, Rizzetto M, Purcell R, Gerin J. Delta hapatitis agent: structural and antigenic properties of the delta-associated particle. Infection and Immunity. 1984;43(3):1000–5.

19. Bonino F, Heermann K, Rizzetto M, Gerlich W. Hepatitis delta virus: protein composition of delta antigen and its hepatitis B virus-derived envelope. Journal of Virology. 1986;58(3):945–50.

20. Farci P. Delta hepatitis: an update. Journal of Hepatology. 2003;39:212–9.

21. Hadler S, De Monzon M, Ponzetto A, Anzola E, Rivero D, Mondolfi A, et al. Delta virus infection and severe hepatitis. An epidemic in the Yucpa Indians of Venezuela. Annals of Internal Medicine. 1984;100(3):339–44.

22. Saracco G, Rosina F, Brunetto M, Amoroso P, Caredda F, Farci P, et al. Rapidly progressive HBsAg-positive hepatitis in Italy. The role of hepatitis delta virus infection. Journal of Hepatology. 1987;5(3):274–81.

23. Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, et al. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. Gut. 2000;46(3):420–6.

24. Yurdaydin C, Idilman R, Bozkaya H, Bozdayi A. Natural history and treatment of chronic delta hepatitis. Journal of Viral Hepatitis. 2010;17(11):749–56.

25. Kew M. Hepatitis viruses (other than hepatitis B and C viruses) as causes of hepatocellular carcinoma : an update.Journal of Viral Hepatitis. 2013;20(3):149–57.

26. Rizzetto M, Ponzetto A, Forzani I. Hepatitis delta virus as a global health problem. Vaccine. 1990;8:S10-14.

27. Sagnelli E, Stroffolini T, Ascione A, Chiararnonte M, Giusti G, Piccinino F, et al. Decrease in HDV endemicity in Italy. Journal of Hepatology. 1997;26(9):20–4.

28. Gaeta G. Chronic Hepatitis D: a vanishing disease? An Italian multicenter study. Hepatology. 2000;32(4):824–7.

29. Gaeta G, Stroffolini T, Smedile A, Niro G, Mele A. Reply : Hepatitis delta in Europe: vanishing or refreshing? To the Editor. Hepatology. 2007;46(4):1312–3.

30. Wedemeyer H, Heidrich B, Manns M. Hepatitis D virus infection-not a vanishing disease in Europe! Hepatology. 2007;45(5):1331–2.

31. Cross T, Rizzi P, Horner M, Jolly A, Hussain M, Smith H, et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. Journal of Medical Virology. 2008;80(2):277–82.

32. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines : Management of chronic hepatitis B virus infection. Journal of Hepatology. 2012;57(1):167–85.

33. Castelnau C, Le Gal F, Ripault M, Gordien E, Martinot-Peignoux M, Boyer N, et al. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up ´. Hepatology. 2006;44:728–35.

34. Erhardt A, Gerlich W, Starke C, Wend U, Donner A, Sagir A, et al. Treatment of chronic hepatitis delta with pegylated interferon- a 2b. Liver International. 2006;26:805–10.

35. Heidrich B, Manns M, Wedemeyer H. Treatment Options for Hepatitis Delta virus infection. Current Infectious Disease Reports. 2013;15(1):31–8.

36. Kamar N, Dalton H, Abravanel F, Izopet J. Hepatitis E virus infection. Clinical Microbiology Reviews. 2014;27(1):116–38.

37. Khuroo M, Teli M, Skidmore S, Sofi M, Khuroo M. Incidence and severity of viral hepatitis in pregnancy. American Journal of Medicine. 1981;70(2):252–5.

38. Kumar A, Beniwal M, Kar P, Sharma JB, Murthy NS. Hepatitis E in pregnancy. International Journal of Gynaecology and Obstetrics. 2004;85(3):240–4.

39. Kamar N, Selves J, Mansuy J, Ouezzani L, Peron J, Guitard J, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. The New England Journal of Medicine. 2008.

40. World Health Organisation. Fact sheet: Hepatitis E [Internet]. 2016 [cited 2017 Jan 3]. Available from: http://www.who.int/mediacentre/factsheets/fs280/en/

41. Liang T. Hepatitis B: the virus and disease. Hepatology. 2009;49(5 Suppl):S13–21.

42. Toy M, Mostert M, de Man R, Richardus J. Transmission routes of hepatitis B virus infection in chronic hepatitis B patients in The Netherlands. Journal of Medical Virology. 2008;80(3):399–404.

43. Trépo C, Chan H, Lok A. Hepatitis B virus infection. Lancet. 2014;384(9959):2053–63.

44. Lavanchy D. Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention. Journal of Clinical Virology. 2005;34 Suppl 1:S1–3.

45. Dienstag J. Hepatitis B virus infection. The New England Journal of Medicine. 2009;359(14):1486–500.

46. Chu C, Liaw Y. Hepatitis B surface antigen seroclearance during chronic HBV infection. Antiviral Therapy. 2010;15(2):133–43.

47. Mcmahon B, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska natives chronically infected with hepatitis B virus. Annals of Internal Medicine. 2001;135(9):759–68.

48. Kwak M, Cho E, Jang E, Lee J, Yu S, Kim Y, et al. Predictors of HBsAg seroclearance in HBeAg-negative chronic hepatitis B patients. Digestion. 2011;84(Supplement 1):23–8.

49. Chu C, Lin D, Liaw Y. Does increased body mass index with hepatic steatosis contribute to seroclearance of hepatitis B virus (HBV) surface antigen in chronic HBV infection? International Journal of Obesity. 2006;871–5.

50. Sánchez-Tapias J, Costa J, Mas A, Bruguera M, Rodes J. Influence of hepatitis B virus genotype on the long-term outcome of chronic hepatitis B in western patients. Gastroenterology. 2002;123(6):1848–56.

51. Liu J, Yang H, Lee M, Lu S, Jen C, Wang L, et al. Incidence and determinants of spontaneous hepatitis B surface antigen seroclearance: a community-based follow-up study. Gastroenterology. 2010;139(2):474–82.

52. Arai M, Togo S, Kanda T, Fujiwara K, Imazeki F, Yokosuka O. Quantification of hepatitis B surface antigen can help predict spontaneous hepatitis B surface antigen seroclearance. European Journal of Gastroenterology & Hepatology. 2012;24(4):414–8.

53. Tseng T, Liu C, Yang H, Su T, Wang C, Chen C, et al. Determinants of spontaneous surface antigen loss in hepatitis B e antigen-negative patients with a low viral load. Hepatology. 2012;55(1):68–76.

54. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. Journal of Viral Hepatitis. 2004;11(2):97–107.

55. Hoofnagle J, Doo E, Liang T, Fleischer R, Lok A. Management of hepatitis B: summary of a clinical research workshop. Hepatology. 2007;45(4):1056–75.

56. Wong G, Wong V, Chan H. Virus and host testing to manage chronic hepatitis B. Clinical Infectious Diseases. 2016;62(Suppl 4).

57. Yim H, Lok A. Natural History of Chronic Hepatitis B Virus Infection: What We Knew in 1981 and What We Know in 2005. Hepatology. 2006;43(2 supplement 1):173–81.

58. McMahon B. The natural history of chronic hepatitis B virus infection. Hepatology. 2009;49(suppl. 5):45–55.

59. Kennedy P, Sandalova E, Jo J, Gill U, Ushiro-Lumb I, Tan A, et al. Preserved T-cell function in children and young adults with immune-tolerant chronic hepatitis B. Gastroenterology. 2012;143:637–45.

60. Hui C, Leung N, Yuen S, Zhang H, Leung K, Lu L, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. Hepatology. 2007;46(2):395–401.

61. Wong G, Chan H, Yu Z, Chan H, Tse C, Wong V. Liver fibrosis progression in chronic hepatitis B patients positive for hepatitis B e antigen: a prospective cohort study with paired transient elastography examination. Journal of Gastroenterology & Hepatology. 2013;28(12):1842–8.

62. Yang L, Zu K, Zhao Y, Wu Z, Chen T, Qin Z, et al. Clinical significance of liver biopsy in chronic hepatitis B patients with persistently normal transaminase. Chinese Journal of Digestive Diseases. 2002;3(4):150–3.

63. Sanchez-Tapias J, Costa J, Mas A, Pares A, Bruguera M, Rodes J. Analysis of factors predicting early seroconversion to anti-HBe in HBeAg-positive chronic hepatitis B. Journal of Hepatology. 1988;6(1):15–22.

64. Yuen M, Yuan H, Wong D, Wong W, Chan A, Wong B, et al. A large population study of spontaneous HBeAg seroconversion and acute exacerbation of chronic hepatitis B infection: implications for antiviral therapy. Gut. 2003;52(3):416–9.

65. Fattovich G. Natural history and prognosis of hepatitis B. Seminars in Liver Disease. 2003;23(1):047–58.

66. Summers J, Connell A, Millman I. Genome of hepatitis B virus : Restriction enzyme cleavage and structure of DNA extracted from Dane particles.Proceedings of the National Academy of Sciences of the United States of America. 1975;72(11):4597–601.

67. Milich D, Liang T. Exploring the biological basis of hepatitis B e antigen in hepatitis B virus infection. Hepatology. 2003;38(5):1075–86.

68. Thimme R, Wieland S, Steiger C, Ghrayeb J, Reimann K, Purcell R, et al. CD8(+) T cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection. Journal of Virology. 2003;77(1):68–76.

69. Bertoletti A, Kennedy P. The immune tolerant phase of chronic HBV infection : new perspectives on an old concept. Cellular& Molecular Immunology. 2015;12(3):258–63.

70. Wherry E. T cell exhaustion. Nature Immunology. 2011;131(6):492–9.

71. Lopes A, Kellam P, Das A, Dunn C, Kwan A, Turner J, et al. Bim-mediated deletion of antigen-specific CD8 T cells in patients unable to control HBV infection. Journal of Clinical Investigation. 2008;118(5):1835–45.

72. Ahmadzadeh M, Johnson L, Heemskerk B, Wunderlich J, Dudley M, White D, et al. Tumor antigen – specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. Blood. 2009;114(8):1537–45.

73. Bengsch B, Martin B, Thimme R. Restoration of HBV-specific CD8+ T-cell function by PD-1 blockade in inactive carrier patients is linked to T-cell differentiation. Journal of Hepatology. 2014;61(6):1212–9.

74. Krummel M, Allison J. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. The Journal of Experimental Medicine. 1996;183(6):2533–40.

75. Schurich A, Khanna P, Lopes A, Han K, Peppa D, Micco L, et al. Role of the coinhibitory receptor cytotoxic T lymphocyte antigen-4 on apoptosis-Prone CD8 T cells in persistent hepatitis B virus infection. Hepatology. 2011;53(5):1494–503.

76. Ye B, Liu X, Li X, Kong H, Tian L, Chen Y. T-cell exhaustion in chronic hepatitis B infection: current knowledge and clinical significance. Cell Death &Disease. 2015;6:e1694.

77. Nebbia G, Peppa D, Schurich A, Khanna P, Singh H, Cheng Y, et al. Upregulation of the Tim-3/Galectin-9 pathway of T Cell exhaustion in chronic hepatitis B virus infection. PLoS One. 2012;7(10):e47648.

78. Sunbul M. Hepatitis B virus genotypes: Global distribution and clinical importance. World Journal of Gastroenterology. 2014;20(18):5427.

79. Chu C, Hussain M, Lok A. Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus genotype C. Gastroenterology. 2002;122(7):1756–62.

80. Nakayoshi T, Maeshiro T, Nakasone H, Sakugawa H, Kinjo F, Orito E, et al. Difference in prognosis between patients infected with hepatitis B virus with genotype B and those with genotype C in the Okinawa Islands: a prospective study. Journal of Medical Virology. 2003;70(3):350–4.

81. Kao J, Chen P, Lai M, Chen D. Hepatitis B virus genotypes and spontaneous hepatitis B e antigen seroconversion in Taiwanese hepatitis B carriers. Journal of Medical Virology.2004;72(3):363–9.

82. Ding X, Mizokami M, Yao G, Xu B, Orito E, Ueda R, et al. Hepatitis B virus genotype distribution among chronic hepatitis B virus carriers in Shanghai, China. Intervirology. 2001;44(1):43–7.

83. Orito E, Ichida T, Sakugawa H, Sata M, Horiike N, Hino K, et al. Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. Hepatology. 2001;34(3):590–4.

84. Wong G, Chan H, Yiu K, Lai J, Chan V, Cheung K, et al. Meta-analysis: the association of hepatitis B virus genotypes and hepatocellular carcinoma. Alimentary Pharmacology & Therapeutics. 2013;37(5):517–26.

85. Gaglio P, Singh S, Degertekin B, Ishitani M, Hussain M, Perrillo R, et al. Impact of the hepatitis B virus genotype on pre-and post-Liver transplantation outcomes. Liver Transplant. 2008;14(10):1420–7.

86. Kao J, Chen P, Lai M, Chen D. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology. 2000;118(3):554–9.

87. Eng H, Lee C, Kuo F, Lu S, Huang C, Tung H, et al. Correlations between hepatitis B virus genotype and cirrhotic or non-cirrhotic hepatoma. Hepato-gastroenterology. 2004;51(56):552–5.

88. Orito E, Mizokami M. Hepatitis B virus genotypes and hepatocellular carcinoma in Japan. Intervirology. 2003;46(6):408–12.

89. Kew M, Kramvis A, Yu M, Arakawa K, Hodkinson J. Increased hepatocarcinogenic potential of hepatitis B virus genotype A in Bantu-speaking sub-saharan Africans. Journal of Medical Virology. 2005;75(4):513–21.

90. Gopalakrishnan D, Keyter M, Shenoy K, Leena K, Thayumanavan L, Thomas V, et al. Hepatitis B virus subgenotype A1 predominates in liver disease patients from Kerala, India. World Journal of Gastroenterology. 2013;19(48):9294.

91. Kumar A, Kumar S, Pandey R, Naik S, Aggarwal R. Hepatitis B virus genotype A is more often associated with severe liver disease in northern India than is genotype D. Indian Journal of Gastroenterology. 2005;24(1):19–22.

92. Thakur V, Guptan R, Kazim S, Malhotra V, Sarin S. Profile, spectrum and significance of HBV genotypes in chronic liver disease patients in the Indian subcontinent. Journal of Gastroenterology & Hepatology. 2002;17(2):165–70.

93. Toan N, Song L, Kremsner P, Duy D, Binh V, Koeberlein B, et al. Impact of the hepatitis B virus genotype and genotype mixtures on the course of liver disease in Vietnam. Hepatology. 2006;43:1375–84.

94. Terrault N, Bzowej N, Chang K, Hwang J, Jonas M, Murad M. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261–83.

95. Sarin S, Kumar M, Lau G, Abbas Z, Chan H, CJ C, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B : a 2015 update. Hepatology International. 2016.

96. Janssen H, Van Zonneveld M, Senturk H, Zeuzem S, Akarca U, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: A randomised trial. Lancet. 2005;365(9454):123–9.

97. Lau G, Piratvisuth T, Luo K, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. The New England Journal of Medicine. 2005;352(26):2682–95.

98. Marcellin P, Lau G, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. The New England Journal of Medicine. 2004;351(12):1206–17.

99. Brook M, Karayiannis P, Thomas H. Which patients with chronic hepatitis B virus infection will respond to alpha-interferon therapy? a statistical analysis of predictive factors. Hepatology. 1989;10(5):761–3.

100. Bonino F, Marcellin P, Lau G, Hadziyannis S, Jin R, Piratvisuth T, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. Gut. 2007;56(5):699–705.

101. Buster E, Hansen B, Lay G, Piratvisuth T, Zeuzem S, Steyerberg E, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon- alfa. Gastroenterology. 2009;137(6):2002–9.

102. Dienstag J, Cianciara J, Karayalcin S, Kowdley K, Willems B, Plisek S, et al. Durability of serologic response after Lamivudine. Hepatology. 2003;37(4):748–55.

103. Poynard T, Hou J, Chutaputti A, Manns M, Naoumov N. Sustained durability of HBEAG seroconversion in chronic hepatitis B patients after treatment with telbuvidine. Journal of Hepatology. 2008;48:S263.

104. Song B, Suh D, Lee H, Chung Y-H, Lee Y. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients With chronic hepatitis B in Korea. Hepatology. 2000;(82):803–6.

105. Jurrien G, Reijnders P, Perquin M, Zhang N, Hansen B, Janssen H. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. Gastroenterology. 2010;139(2):491–8.

106. Kim G, Lim Y, An J, Lee D, Shim J, Kim K, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut [Internet]. 2014;63(8):1325–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24162593

107. Arase Y, Ikeda K, Suzuki F, Suzuki Y, Saitoh S, Kobayashi M, et al. Long-term outcome after hepatitis B surface antigen seroclearance in patients with chronic hepatitis B. American Journal of Medicine. 2006;119(71):9–17.

108. Yuen M, Wong D, Fung J, Ip P, But D, Hung I, et al. HBsAg seroclearance in chronic hepatitis B in Asian patients : replicative level and risk of hepatocellular carcinoma. Gastroenterology. 2008;135(4):1192–9.

109. Hadziyannis S, Tassopoulos J, Heathcote E, Chang T, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology. 2006;131(6):1743–51.

110. Chang T, Liaw Y, Wu S, Schiff E, Han K, Lai C, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology. 2010;52(3):886–93.

111. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson I, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B : a 5-year open-label follow-up study. Lancet. 2013;381:468–75.

112. Thomas D. Global control of hepatitis C : where challenge meets opportunity. Nature Medicine. 2013;19(7):850–8.

113. Sherlock S. Hepatitis C virus: a historical perspective. Digestive Diseases and Sciences. 1996;41(12):S3–5.

114. Martell M, Esteban J, Quer J, Genescà J, Weiner A, Esteban R, et al. Hepatitis C virus (HCV) circulates as a population of different but closely related genomes: quasispecies nature of HCV genome distribution. Journal of Virology. 1992;66(5):3225–9.

115. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. Journal of Hepatology. 2014;61(1):S45–57.

116. Hanafiah K, Groeger J, Flaxman A, Wiersma S. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57(4):1333–42.

117. Messina J, Humphreys I, Flaxman A, Brown A, Cooke G, Pybus O, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77–87.

118. Castillo I, Rodríguez-Iñigo E, Bartolomé J, de Lucas S, Ortíz-Movilla N, López-Alcorocho J, et al. Hepatitis C virus replicates in peripheral blood mononuclear cells of patients with occult hepatitis C virus infection. Gut. 2005;54(5):682–5.

119. Barth H, Liang T, Baumert T. Hepatitis C virus entry: molecular biology and clinical implications. Hepatology. 2006;44(3):527–35.

120. Ploss A, Evans M. Hepatitis C virus host cell entry. Current Opinion in Virology. 2012;2(1):14–9.

121. Lindenbach BD, Rice CM. Unravelling hepatitis C virus replication from genome to function. Nature. 2005; 436 (7053):933-8

122. Bartenschlager R, Lohmann V. Replication of hepatitis c virus. Journal of General Virology. 2000;81(part 7): 1631-48.

123. Petrovic D, Dempsey E, Doherty DG, Kelleher D, Long A. Hepatitis C virus - T cell responses and viral escape mutations. European Journal of Immunology. 2012;42(1):17-26

124. Herker E, Ott M. Unique ties between hepatitis C virus replication and intracellular lipids. Trends in Endocrinology and Metabolism. 2011;22(6):241–8.

125. Hoofnagle J. Course and outcome of hepatitis C. Hepatology. 2002;36(5):ajhep0360s21.

126. King S, Adjei-Asante K, Appiah L, Adinku D, Beloukas A, Atkins M, et al. Antibody screening tests variably overestimate the prevalence of hepatitis C virus infection among HIV-infected adults in Ghana. Journalof Viral Hepatitis. 2015;22(5):461–8.

127. Chan T, Lok A, Cheng I, Chan R. Prevalence of hepatitis C virus infection in hemodialysis patients: a longitudinal study comparing the results of RNA and antibody assays. Hepatology. 1993;17(1):5–8.

128. Lok A, Ma O, Chan T, Lai C, Chung H, Ng C, et al. Overestimation of the prevalence of antibody to hepatitis C virus in retrospective studies on stored sera. Hepatology. 1991;14(5):756–62.

129. Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, Trepo C. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. Journal of Viral Hepatitis. 2001;8(2):87–95.

130. Abdel-Hamid M, El-daly M, El-kafrawy S, Mikhail N, Strickland G, Fix A. Comparison of second- and third-generation enzyme immunoassays for detecting antibodies to hepatitis C virus. Journal of Clinical Microbiology 2002;40(5):1656–9.

131. Kamili S, Drobeniuc J, Araujo A, Hayden T. Laboratory diagnostics for hepatitis C virus infection. Clinical Infectious Diseases. 2012;55(Suppl 1):43–8.

132. Lavanchy D. The global burden of hepatitis C. Liver International. 2009;29:74–81.

133. Alter M, Kruszon-Moran D, Nainan O, McQuillan G, Gao F, Moyer L, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. The New England Journal of Medicine. 1999;341(8):556–62.

134. Maheshwari A, Ray S, Thuluvath P. Acute hepatitis C. Lancet. 2008;372(9635):321–32.

135. Wasley A, Alter M. of hepatitis C: geographic differences and temporal trends. Seminars in Liver Disease. 2000;20(1):1–16.

136. Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. Intervirology. 2010;53(1):39–43.

137. Mellor J, Holmes E, Jarvis L, Yap P, Simmonds P. Investigation of the pattern of hepatitis C virus sequence diversity in different geographical regions: implications for virus classification. The International HCV Collaborative Study Group. Journal of General Virology. 1995;76 (Pt 10):2493–507.

138. Frank C, Mohamed M, Strickland G, Lavanchy D, Arthur R, Magder L, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet. 2000;355(9207):887–91.

139. Guerra J, Garenne M, Mohamed M, Fontanet A. HCV burden of infection in Egypt: results from a nationwide survey. Journal of Viral Hepatitis. 2012;19(8):560–7.

140. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clinical Infectious Diseases. 2009;49(4):561–73.

141. Patrick D, Tyndall M, Cornelisse P, Li K, Sherlock C, Rekart M, et al. Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection. Canadian Medical Association Journal. 2001;165(7):889–95.

142. Miller C, Spittal P, Frankish J, Li K, Schechter M, Wood E. HIV and hepatitis C outbreaks among high-risk youth in Vancouver demands a public health response. Canadian Journal of Public Health Rev Can santé publique. 2005;96(2):107–8.

143. Roy E, Alary M, Morissette C, Leclerc P, Boudreau J, Parent R, et al. High hepatitis C virus prevalence and incidence among Canadian intravenous drug users. International Journal of STD &AIDS. 2007;18(1):23–7.

144. Hagan H, Pouget E, Des Jarlais D, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. American Journal of Epidemiology. 2008;168(10):1099–109.

145. World Health Organisation. Fact sheet: Blood safety and availability [Internet]. 2016 [cited 2017 Jan 5]. Available from: http://www.who.int/mediacentre/factsheets/fs279/en/

146. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of bloodborne pathogens: A review. Bulletin of the World Health Organisation. 1999;77(10):789–800.

147. Okwen M, Ngem B, Alomba F, Capo M, Reid S, Ewang E. Uncovering high rates of unsafe injection equipment reuse in rural Cameroon: validation of a survey instrument that probes for specific misconceptions. Harm Reduction Journal 2011;8(1):4.

148. Reeler A. Injections: A fatal attraction? Social Sciences&Medicine. 1990;31(10):1119–25.

149. Luby S, Qamruddin K, Shah A, Omair A, Pahsa O, Khan A, et al. The relationship between therapeutic injections and high prevalence of hepatitis C infection in Hafizabad, Pakistan. Epidemiology and Infection. 1997;119(3):349–56.

150. Vandelli C, Renzo F, Romanò L, Tisminetzky S, De Palma M, Stroffolini T, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. American Journal of Gastroenterology. 2004;99(5):855–9.

151. Terrault N, Dodge J, Murphy E, Tavis J, Kiss A, Levin T, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: The HCV partners study. Hepatology. 2013;57(3):881–9.

152. Salleras L, Bruguera M, Vidal J, Plans P, Domı A, Navas E, et al. Importance of sexual transmission of hepatitis C virus in seropositive pregnant women: a case-control study. Journal of Medical Virology 1997;167:164–7.

153. Danta M, Brown D, Bhagani S, Pybus O, Sabin C, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS. 2007;21(8):983–91.

154. Bottieau E, Apers L, Van Esbroeck M, Vandenbruaene M, Florence E. Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001-2009. Euro Surveillance. 2010;15(39):19673.

155. Jin F, Prestage G, Matthews G, Zablotska I, Rawstorne P, Kippax S, et al. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV-negative and HIV-positive men in Sydney, Australia. Journal of Sexually Transmitted Infections. 2010;86(1):25–8.

156. Benova L, Mohamoud Y, Calvert C, Abu-raddad L. Vertical transmission of hepatitis C virus : systematic rReview and meta-analysis. Clinical Infectious Diseases. 2014;59(6):765–73.

157. Grebely J, Page K, Sacks-Davis R, van der Loeff M, Rice T, Bruneau J, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology. 2013;109–20.

158. Wang C, Krantz E, Klarquist J, Krows M, McBride L, Scott E, et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. Journal of Infectious Diseases. 2007;196(10):1474–82.

159. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. The New England Journal of Medicine. 1999;340(16):1228–33.

160. Vogt M, Lang T, Frösner G, Klingler C, Sendl A, Zeller A, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. The New England Journal of Medicine. 1999;341:866–70.

161. Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Crocè LS, Mazzoran L, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. Gut. 1999;44(6):874–80.

162. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. Hepatology. 2000;32(1):91–6.

163. Hayashi J, Kishihara Y, Ueno K, Yamaji K, Kawakami Y, Furusyo N, et al. Age-related response to interferon alfa treatment in women vs men with chronic hepatitis C virus infection. Archivesof Internal Medicine. 1998;158(2):177–81.

164. Villano S, Vlahov D, Nelson K, Cohn S, Thomas D. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999;29(3):908–14.

165. Thomas D, Thio C, Martin M, Qi Y, Ge D, O'hUigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798–801.

166. Thomas D, Astemborski J, Rai R, Anania F, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection. American Medical Association. 2000;284(4):450–6.

167. Serfaty L, Aumaître H, Chazouillères O, Bonnand A, Rosmorduc O, Poupon R, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology. 1998;27(5):1435–40.

168. El-Serag H. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology. 2002;36(5):74–83.

169. Tong M, El-Farra NS, Reikes A, Co RL. Clinical outcomes after transfusion-associated hepatitis C. The New England Journal of Medicine. 1995;332(22):1463–6.

170. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349(9055):825–32.

171. Peters M, Terrault N. Alcohol use and hepatitis C. Hepatology. 2002;36(5 Suppl 1):S220-5.

172. Missiha S, Ostrowski M, Heathcote E. Disease progression in chronic hepatitis C: modifiable and nonmodifiable factors. Gastroenterology. 2008;134(6):1699–714.

173. Bochud P, Cai T, Overbeck K, Bochud M, Dufour J, Müllhaupt B, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. Journal of Hepatology. 2009;51(4):655–66.

174. Yano M, Kumada H, Kage M, Ikeda K, Shimamatsu K, Inoue O, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology. 1996;23:1334–40.

175. Ryder S, Irving W, Jones D, Neal K, Underwood J. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. Gut. 2004;53:451–5.

176. Datz C, Cramp M, Haas T, Dietze O, Nitschko H, Froesner G, et al. The natural course of hepatitis C virus infection 18 years after an epidemic outbreak of non-A, non-B hepatitis in a plasmapheresis centre. Gut. 1999;44(4):563–7.

177. Matsumura H, Moriyama M, Goto I, Tanaka N, Okubo H, Arakawa Y. Natural course of progression of liver fibrosis in Japanese patients with chronic liver disease type C-a study of 527 patients at one establishment. Journal of Viral Hepatitis. 2000;7(4):268–75.

178. Yi Q, Wang P, Krahn M. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. Journal of Viral Hepatitis. 2004;11(2):166–74.

179. Amin J, Law M, Bartlett M, Kaldor J, Dore G. Causes of death after diagnosis of hepatitis B or hepatitis C infection : a large community-based linkage study. Lancet. 2006;368:938–45.

180. Neal K, Ramsay S, Thomson B, Irving W. Excess mortality rates in a cohort of patients infected with the hepatitis C virus: a prospective study. Gut. 2007;56(8):1098–104.

181. Kielland K, Skaug K, Amundsen E, Dalgard O. All-cause and liver-related mortality in hepatitis C infected drug users followed for 33 years: a controlled study. Journal of Hepatology. 2013;58(1):31–7.

182. Seeff L. Natural history of chronic hepatitis C. Hepatology. 2002;36(5):35–46.

183. Cauch-Dudek K, Abbey S, Stewart D, Heathcote E. Fatigue in primary biliary cirrhosis. Gut. 1998;43(5):705–10.

184. Poupon R, Chrétien Y, Chazouillères O, Poupon R, Chwalow J. Quality of life in patients with primary biliary cirrhosis. Hepatology. 2004;40(2):489–94.

185. Rannard A, Buck D, Jones D, James O, Jacoby A. Assessing quality of life in primary biliary cirrhosis. Clinical Gastroenterology and Hepatology.2004;2(2):164–74.

186. Barkhuizen A, Rosen H, Wolf S, Flora K, Benner K, Bennett R. Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients. American Journal of Gastroenterology. 1999;94(5):1355–60.

187. Poynard T, Cacoub P, Ratziu V, Myers R, Dezailles M, Mercadier A, et al. Fatigue in patients with chronic hepatitis C. Journal of Viral Hepatitis. 2002;9:295–303.

188. Cacoub P, Gragnani L, Comarmond C, Zignego A. Extrahepatic manifestations of chronic hepatitis C virus infection. Digestive and Liver Disease. 2014;46:165–73.

189. Swain M. Fatigue in chronic disease. Clinical Science. 2000;99:1–8.

190. Sherlock S, Summerskill W, White L, Phear E. Portal–systemic encephalopathy; neurological complications of liver disease. Lancet. 1954;267(6836):454–7.

191. Ferenci P. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th world congresses of gastroenterology, Vienna, 1998. Hepatology. 2002;35(3):716–21.

192. Weissenborn K, Heidenreich S, Ennen J, Rückert N, Hecker H. Attention deficits in minimal hepatic encephalopathy. Metabolic Brain Disease. 2001;16(1/2):13–9.

193. Forton D, Thomas H, Murphy C, Allsop J, Foster G, Main J, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. Hepatology. 2002;35(2):433–9.

194. Hilsabeck R, Perry W, Hassanein T. Neuropsychological impairment in patients with chronic hepatitis C. Hepatology. 2002;35(2):440–6.

195. Kramer L, Bauer E, Funk G, Hofer H, Jessner W, Steindl-Munda P, et al. Subclinical impairment of brain function in chronic hepatitis C infection. Journal of Hepatology. 2002;37(3):349–54.

196. Córdoba J, Flavià M, Jacas C, Sauleda S, Esteban J, Vargas V, et al. Quality of life and cognitive function in hepatitis C at different stages of liver disease. Journal of Hepatology. 2003;39:231–8.

197. Hilsabeck R, Hassanein T, Carlson M, Ziegler E, Perry W. Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C. Journal of the International Neuropsychological Society. 2003;9(6):847–54.

198. Forton D, Hamilton G, Allsop J, Grover V, Wesnes K, O'Sullivan C, et al. Cerebral immune activation in chronic hepatitis C infection: A magnetic resonance spectroscopy study. Journal of Hepatology. 2008;49(3):316–22.

199. Gallegos-Orozco J, Fuentes A, Argueta J, Pérez-Pruna C, Hinojosa-Becerril C, Sixtos-Alonso M, et al. Health-related quality of life and depression in patients with chronic hepatitis C. Archives of Medical Research. 2003;34:124–9.

200. Dwight M, Kowdley K, Russo J, Ciechanowski P, Larson A, Katon W. Depression, fatigue, and functional disability in patients with chronic hepatitis C. Journal of Psychosomatic Research. 2000;49(5):311–7.

201. Fontana R, Hussain K, Schwartz S, Moyer C, Su G, Lok A. Emotional distress in chronic hepatitis C patients not receiving antiviral therapy. Journal of Hepatology. 2002;36(3):401–7.

202. Carta M, Hardoy M, Garofalo A, Pisano E, Nonnoi V, Intilla G, et al. Association of chronic hepatitis c with major depressive disorders: irrespective of interferonalpha therapy. Clinical Practice and Epidemiology in Mental Health. 2007;3(22):1–4.

203. Davis G, Balart L, Schiff E, Lindsay K, Bodenheimer H, Perrillo R, et al. Assessing health-related quality of life in chronic hepatitis C using the Sickness Impact Profile. Clinical Therapeutics. 1994;16(2):334–43.

204. Carithers R, Sugano D, Bayliss M. Health assessment for chronic HCV infection: results of quality of life. Digestive Diseases and Sciences. 1996;41(12 suppl):75S–80S.

205. Bonkovsky H, Woolley J. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. Hepatology. 1999;29(1):264–70.

206. Ware J, Bayliss M, Mannocchia M, Davis G. Health-Related Quality of Life in chronic hepatitis C : impact of disease and treatment response. Hepatology. 1999;30(2):550–5.

207. Foster G, Goldin R, Thomas H. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology. 1998;27(1):209–12.

208. Lipsitz J, Williams J, Rabkin J, Remien R, Bradbury M, el Sadr W, et al. Psychopathology in male and female intravenous drug users with and without HIV infection. American Journal of Psychiatry. 1994;151(11):1662–8.

209. Kendall J, Sherman M, Bigelow G. Psychiatric Symptoms in Polysubstance Abusers: Relationship to Race, Sex, and Age. Addictive Behaviours. 1995;20(5):685–90.

210. McHutchison J, Ware J, Bayliss M, Pianko S, Albrecht J, Cort S, et al. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. Journal of Hepatology. 2001;34(1):140–7.

211. Bini E, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. Alimentary Pharmacology and Therapeutics. 2006;23(6):777–85.

212. Hollander A, Foster G, Weiland O. Health-related quality of life before, during and after combination therapy with interferon and ribavirin in unselected Swedish patients with chronic hepatitis C. Scandinavian Journal of Gastroenterology. 2006;41(5):577–85.

213. Bonkovsky H, Snow K, Malet P, Back-Madruga C, Fontana R, Sterling R, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. Journal of Hepatology. 2007;46(3):420–31.

214. Quarantini L, Miranda-Scippa A, Batista-Neves S, Galvao-de-Almeida A, Lacerda A, Moriyama T, et al. The effect of early virological response in health-related quality of life in HCV-infected patients. Journal of Medical Virology. 2008;80(3):419–23.

215. Rodger A, Jolley D, Thompson S, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C virus on quality of life. Hepatology. 1999;30(5):1299–301.

216. Conrad S, Garrett L, Cooksley W, Dunne M, MacDonald G. Living with chronic hepatitis C means “you just haven't got a normal life any more". Chronic Illness. 2006;2(2):121–31.

217. Swain M, Lai M, Shiffman M, Cooksley W, Zeuzem S, Dieterich D, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology. 2010;139(5):1595–601.

218. Poynard T, McHutchinson J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology. 2002;122(5):1303–13.

219. van der Meer A, Veldt B, Feld J, Wedemeyer H, Dufour J, Lammert F, et al. Association between sustained virological and advanced hepatic fibrosis. The Journal of the American Medical Association. 2012;308(24):2584–93.

220. Morgan R, Baack B, Smith B, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Annals of Internal Medicine. 2013;158(5 Pt 1):329–37.

221. Feld J, Hoofnagle J. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. Nature. 2005;436(7053):967–72.

222. Konerman M, Mehta S, Sutcliffe C, Vu T, Higgins Y, Torbenson M, et al. Fibrosis progression in human immunodeficiency virus/hepatitis C Virus coinfected adults: prospective analysis of 435 liver biopsy pairs. Hepatology. 2014;59(3):767–75.

223. Jacobson I, McHutchison J, Dusheiko G, Di Bisceglie A, Reddy K, Bzowej N, et al. ADVANCE Study. Telaprevir for previously untreated chronic hepatitis C virus infection. The New England Journal of Medicine. 2011;364:2405–16.

224. Poordad F, McCone J, Bacon B, Bruno S, Manns M, Sulkowski M, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection. The New England Journal of Medicine. 2011;364(13):1195–206.

225. Di Bisceglie A, Hoofnagle J. Optimal therapy of hepatitis C. Hepatology. 2002;36(5 Suppl 1):S121-7.

226. Zeuzem S, Feinman S, Rasenack J, Heathcote E, Lai M, Gane E, et al. Peginterferon alpha-2a in patients with chronic hepatitis C. The New England Journal of Medicine. 2000;343(23):1666–72.

227. Fried M, Shiffman M, Reddy K, Smith C, Marinos G, Gonçales F, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis c virus infection. The New England Journal of Medicine. 2002;347(13):975–82.

228. Hadziyannis S, Sette H, Morgan T, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Annals of Internal Medicine. 2004;140:346–55.

229. Keeffe E. Chronic hepatitis C: management of treatment failures. Clinical Gastroenterology and Hepatology. 2005;10(2):102–5.

230. Ghany M, Strader D, Thomas D, Seeff L. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49(4):1335–74.

231. Fried M, Hadziyannis S, Shiffman M, Messinger D, Zeuzem S. Rapid virological response is the most important predictor of sustained virological response across genotypes in patients with chronic hepatitis C virus infection. Journal of Hepatology. 2011;55(1):69–75.

232. Shiffman M. Chronic hepatitis C : treatment of pegylated interferon / ribavirin nonresponders. Current Hepatitis Reports. 2006;5(3):114–20.

233. Pearlman B, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clinical Infectious Diseases. 2011;52(7):889–900.

234. Pawlotsky J, Aghemo A, Back D, Dusheiko G, Forns X, Puoti M, et al. EASL Recommendations on Treatment of Hepatitis C 2014. Journal of Hepatology. 2015;63:199–236.

235. Dienstag J, McHutchison J. American gastroenterological association technical review on the management of hepatitis C. Gastroenterology. 2006;130(1):231–64.

236. Fattovich G, Giustina G, Favarato S, Ruol A. A survey of adverse events in 11 241 patients with chronic viral hepatitis treated with alfa interferon. Journal of Hepatology. 1996;24:38–47.

237. McDonald E, Mann A, Thomas H. Interferons as mediators of psychiatric morbidity. An investigation in a trial of recombinant alpha-interferon in hepatitis-B carriers. Lancet. 1987;2(8569):1175–8.

238. Renault P, Hoofnagle J, Park Y, Mullen K, Peters M, Jones D, et al. Psychiatric complications of long-term interferon alfa therapy. Archives of Internal Medicine. 1987;147(9):1577–80.

239. Ho S, Nguyen H, Tetrick L, Opitz G, Basara M, Dieperink E. Influence of psychiatric diagnoses on interferon-alpha treatment for chronic hepatitis C in a veteran population. American Journal of Gastroenterology. 2001;96(1):157–64.

240. Janssen H, Brouwer J, Mast R, Van Der Schalm S. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. Journal of Hepatology. 1994;21(2):241–3.

241. Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, Schindlbeck N, et al. Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. Hepatology. 2003;37(2):443–51.

242. Allison M, Wreghitt T, Palmer C, Alexander G. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. Journal of Hepatology. 1994;21(6):1135–9.

243. Mehta S, Brancati F, Sulkowski M, Strathdee S, Szklo M, Thomas D. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Annals of Internal Medicine. 2000;133(8):592–9.

244. Naing C. Relationship between hepatitis C virus infection and type 2 diabetes mellitus: meta-analysis. World Journal of Gastroenterology. 2012;18(14):1642.

245. Fabris P, Betterle C, Floreani A, Greggio N, de Lazzari F, Naccarato R, et al. Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. Lancet. 1992;340(8818):548.

246. Bosi E, Minelli R, Bazzigaluppi E, Salvi M. Fulminant autoimmune Type 1 diabetes during interferon-alpha therapy: a case of Th1-mediated disease? Diabetic Medicine. 2001;18(4):329–32.

247. Cozzolongo R, Betterle C, Fabris P, Paola Albergoni M, Lanzilotta E, Manghisi O. Onset of type 1 diabetes mellitus during peginterferon alpha-2b plus ribavirin treatment for chronic hepatitis C. European Journal of Gastroenterology & Hepatology. 2006;18(6):689–92.

248. Schreuder T, Gelderblom H, Weegink C, Hamann D, Reesink H, Hans DeVries J, et al. High incidence of type 1 diabetes mellitus during or shortly after treatment with pegylated interferon alpha for chronic hepatitis C virus infection. Liver International. 2008;28(1):39–46.

249. Nakamura K, Kawasaki E, Imagawa A, Awata T, Ikegami H, Uchigata Y, et al. Type 1 diabetes and interferon therapy: A nationwide survey in Japan. Diabetes Care. 2011;34:2084–9.

250. Okanoue T, Sakamoto S, Itoh Y, Minami M, Yasui K, Sakamoto M, et al. Side effects of high-dose interferon therapy for chronic hepatitis C. Journal of Hepatology. 1996;25(3):283–91.

251. Mandac J, Chaudhry S, Sherman K, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. Hepatology. 2006;43(4):661–72.

252. Bacon BR, Gordon S, Lawitz E. Boceprevir for previously treated chronic HCV genotype 1 infection. The New England Journal of Medicine. 2011;364(13):1207–17.

253. Hézode C. Boceprevir and telaprevir for the treatment of chronic hepatitis C: safety management in clinical practice. Liver International. 2012;32 Suppl 1:32–8.

254. Maasoumy B, Port K, Markova A, Serrano B, Rogalska-Taranta M, Sollik L, et al. Eligibility and safety of triple therapy for hepatitis C: lessons learned from the first experience in a real world setting. PLoS One. 2013;8(2):e55285.

255. Izquierdo L, Helle F, Francois C, Castelain S, Duverlie G, Brochot E. Simeprevir for the treatment of hepatitis C virus infection. Pharmacogenomics and Personalised Medicine. 2014;7:241–9.

256. Belda O, Targett-Adams P. Small molecule inhibitors of the hepatitis C virus-encoded NS5A protein. Virus Research. 2012;170(1–2):1–14.

257. Pawlotsky J. NS5A inhibitors in the treatment of hepatitis C. Journal of Hepatology. 2013;59(2):375–82.

258. Nelson D, Cooper J, Lalezari J, Lawitz E, Pockros P, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61(4):1127–35.

259. Hundt J, Li Z, Liu Q. Post-translational modifications of hepatitis C viral proteins and their biological significance. World Journal of Gastroenterology. 2013;19(47):8929–39.

260. Jacobson I, Dore G, Foster G, Fried M, Radu M, Rafalsky V, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet. 2014;384(9941):403–13.

261. Manns M, Marcellin P, Poordad F, Stanislau E, Buti M, Horsmans Y, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2014;384(9941):414–26.

262. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki J, Andreone P, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology. 2014;146(7):1669–1679.e3.

263. Hayashi N, Izumi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, et al. Simeprevir with peginterferon / ribavirin for treatment-naïve hepatitis C genotype 1 patients in Japan : CONCERTO-1 , a phase III trial. Journal of Hepatology. 2014;61(2):219–27.

264. Moreno C, Hezode C, Marcellin P, Bourgeois S, Francque S, Samuel D, et al. Efficacy and safety of simeprevir with PegIFN / ribavirin in naïve or experienced patients infected with chronic HCV genotype 4 q. Journal of Hepatology. 2015;62(5):1047–55.

265. Lawitz E, Mangia A, Wyles D, Rodriguez-torres M, Hassanein T, Gordon S, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. The New England Journal of Medicine. 2013;368(20):1878–87.

266. Afdhal N, Reddy K, Nelson D, Lawitz E, Gordon S, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. The New England Journal of Medicine. 2014;370(16):1483–93.

267. Sulkowski M, Gardiner D, Rodriguez-torres M, Reddy K, Hassanein T, Jacobson I, et al. Daclatasvir plus Sofosbuvir for previously treated or untreated chronic HCV infection. The New England Journal of Medicine. 2014;370(3):211–21.

268. Lawitz E, Sulkowski M, Reem G, Rodriguez-torres M, Younossi Z, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014;384(9956):1756–65.

269. Jacobson I, Gordon S, Kowdley K, Yoshida E, Rodriguez-torres M, Sulkowski M, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. The New England Journal of Medicine. 2013;368(20):1867–77.

270. Zeuzem S, Dusheiko G, Salupere R, Mangia A, Flisiak R, Hyland R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. The New England Journal of Medicine. 2014;370(21):1993–2001.

271. Omata M, Nishiguchi S, Ueno Y, Mochizuki H, Izumi N, Ikeda F, et al. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection : an open-label , phase 3 trial. Journal of Viral Hepatitis. 2014;21(11):762–8.

272. Foster GR, Pianko S, Brown A, Forton D, Nahass RG, George J, Barnes E et al. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. Gastroenterology. 2015; 149(6):1462-70

273. Dubin P, Sclair S, Rico R, Boehme A, Chen E, Martin P, et al. Low SVR rates in Clinical Practice for treating genotype 1 chronic hepatitis C with protease inhibitors boceprevir and telaprevir. Digestive Diseases and Sciences. 2015;60(1):272–4.

274. Terrault N, Zeuzem S, Di Bisceglie A, Lim J, Pockros P, Frazier L, et al. Treatment Outcomes With 8, 12 and 24 Week Regimens of ledipasvir/sofosbuvir for the treatment of hepatitis C infection: analysis of a multicenter prospective, observational study.The 66th Annual Meeting of the American Association for the Study of Liver Diseases. 2015.

275. Trio Health Platform. Trio Health Platform website [Internet]. 2015 [cited 2017 Jan 11]. Available from: http://triohealth.com/

276. Curry M, Bacon B, Dieterich D, Flamm S, Guest L, Kowdley K, et al. Effectiveness of 8 or 12 week LDV-SOF in treatment-naïve atients with non-cirrhotic, genotype 1 hepatitis C: real-world experience from the TRIO network.The 66th Annual Meeting of the American Association for the Study of Liver Diseases. 2015;

277. Younossi Z, Park H, Gordon S, Ferguson J, Ahmed A, Dieterich D, et al. Real-world outcomes of ledipasvir/sofosbuvir in treatment-naïve patients with hepatitis C. American Journal of Managed Care. 2016;22(6):205–11.

278. Welzel T, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, et al. Daclatasvir plus sofosbuvir , with or without ribavirin , achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut. 2016;65:1861–70.

279. Foster G, Irving W, Cheung M, Walker A, Hudson B, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. Journal of Hepatology. 2016;64(6):1224–31.

280. Ferrarese A, Zanetto A, Gambato M, Bortoluzzi I, Nadal E, Germani G, et al. Liver transplantation for viral hepatitis in 2015. World Journal of Gastroenterology. 2016;22(4):1570–81.

281. Ballardini G, De Raffele E, Groff P, Bioulac-Sage P, Grassi A, Ghetti S, et al. Timing of reinfection and mechanisms of hepatocellular damage in transplanted hepatitis C virus – reinfected liver. Liver Transplant. 2002;8(1):10–20.

282. Berenguer M, Rayon J, Mora J, Pastor M, Oritz V, Carrasco D, et al. Natural history of clinically compensated hepatitis C virus – related graft cirrhosis after liver transplantation. Hepatology. 2000;32(3):852–8.

283. Roche B, Samuel D. Risk factors for hepatitis C recurrence after liver transplantation. Journal of Viral Hepatitis. 2007;14(Suppl 1):89–96.

284. Oliver M, Ortiz C, Ortiz J. Challenging hepatitis C-infected liver transplant patients. Hepatic Medicine: Evidence and Research. 2016;8:1–8.

285. Costella A, Goldberg D, Harris H, Hutchinson S, Jessop L, Lyons M, et al. Public Health England Hepatitis C in the UK 2015 report. 2015.

286. Department of Health. Hepatitis C Strategy for England. 2002.

287. D'Souza R, Glynn M, Alstead E, Osonayo C, Foster G. Knowledge of chronic hepatitis C among East London primary care physicians following the Department of Health's educational campaign. QJM: An International Journal of Medicine. 2004;97(6):331–6.

288. Hawkes N. Confronting the silent epidemic : a critical review of hepatitis C management in the UK. 2013.

289. Wilson J. Principles of Screening for Disease. Proceedings of the Royal Society of Medicine. 1971;64:1255–6.

290. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease [Internet]. 1998 [cited 2017 Jan 1]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm

291. Smith B, Morgan R, Beckett G, Falck-Ytter Y, Holtzman D. Clinical guideline hepatitis C virus testing of persons born during 1945 – 1965 : Recommendations from the Centers for Disease Control and Prevention. Annals of Internal Medicine. 2012;157(11):817–23.

292. Koretz R, Lin K, Ioannidis J, Lenzer J. Is widespread screening for hepatitis C justified? British Medical Journal. 2015;350:1–4.

293. Freeman A. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001;34(4):809–16.

294. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.

295. Lee M, Yang H, Lu S, Jen C, You S, Wang L, et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. Journal of Infectious Diseases. 2012;206(4):469–77.

296. Rein D, Smith B, Wittenborn J, Lesesne S, Wagner L, Roblin D, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S primary care settings. Annals of Internal Medicine. 2012;156(4):263–70.

297. Wong W, Tu H, Feld J, Wong T, Krahn M. Cost-effectiveness of screening for hepatitis C in Canada. Canadian Medical Association Journal. 2015;187(3):E110–21.

298. National Institute For Health And Care Excellence. Hepatitis B and C testing : people at risk of infection. London; 2012.

299. European Association For The Study Of The Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. Journal of Hepatology. 2014;60(2):392–420.

300. Batash S, Khaykis I, Raicht R, Bini E. High prevalence of hepatitis C virus infection among immigrants from the former Soviet Union in the New York City metropolitan area: results of a community-based screening program. American Journal of Gastroenterology. 2008;103(4):922–7.

301. Uddin G, Shoeb D, Solaiman S, Marley R, Gore C, Ramsay M, et al. Prevalence of chronic viral hepatitis in people of south Asian ethnicity living in England: the prevalence cannot necessarily be predicted from the prevalence in the country of origin. Journal of Viral Hepatitis. 2010;17(5):327–35.

302. Hwang J, Mohseni M, Gor B, Wen S, Guerrero H, Vierling J. Hepatitis B and hepatitis C prevalence and treatment referral among Asian Americans undergoing community-based hepatitis screening. American Journal of Public Health. 2010;100(S1):S118–24.

303. Richter C, Ter Beest G, Sancak I, Aydinly R, Bulbul K, Laetemia-Tomata F, et al. Hepatitis B prevalence in the Turkish population of Arnhem: implications for national screening policy? Epidemiology & Infection. 2012;140(4):724–30.

304. Richter C, Ter Beest G, Gisolf E, Van Bentum P, Waegemaekers C, Swanink C, et al. Screening for chronic hepatitis B and C in migrants from Afghanistan, Iran, Iraq, the former Soviet Republics, and Vietnam in the Arnhem region, The Netherlands. Epidemiology & Infections. 2014;142(10):2140–6.

305. Pavlin N, Gunn J, Parker R, Fairley C, Hocking J. Implementing chlamydia screening: what do women think? a systematic review of the literature. BMC Public Health. 2006;6:221.

306. Vernon S. Participation in colorectal cancer screening: a review. Journal of the National Cancer Institute. 1997;89(19):1406–22.

307. Nazroo J. The structuring of ethnic inequalities in health: economic position, racial discrimination, and racism. American Journal of Public Health. 2003;93(2):277–84.

308. Hoare T. Breast screening and ethnic minorities. Cancer. 1996;41:38–41.

309. Sutton G, Storer A, Rowe K. Cancer screening coverage of south Asian women in Wakefield. Journal of Medical Screening. 2001;8(4):183–6.

310. Robb K, Solarin I, Power E, Atkin W, Wardle J. Attitudes to colorectal cancer screening among ethnic minority groups in the UK. BMC Public Health. 2008;8:34.

311. Weech-Maldonado R, Morales L, Elliott M, Spritzer K, Marshall G, Hays R. Race/ethnicity, language, and patients' assessments of care in medicaid managed care. Health Services Research Journal. 2003;38:789–808.

312. Mead N, Roland M. Understanding why some ethnic minority patients evaluate medical care more negatively than white patients: a cross sectional analysis of a routine patient survey in English general practices. British Medical Journal. 2009;339:b3450.

313. Szczepura A. Access to health care for ethnic minority populations. Postgraduate Medical Journal. 2005;81:141–8.

314. Tarrant C, Stokes T, Baker R. Factors associated with patients' trust in their general practitioner: a cross-sectional survey. British Journal of General Practice. 2003;53(495):798–800.

315. Carpenter W, Godley P, Clark J, Talcott J, Finnegan T, Mishel M, et al. Racial differences in trust and regular source of patient care and the implications for prostate cancer screening use. Cancer. 2009;115(21):5048–59.

316. Wasserman J, Flannery M, Clair J. Raising the ivory tower: the production of knowledge and distrust of medicine among African Americans. Journal of Medical Ethics. 2007;33(3):177–80.

317. Caruana S, Kelly H, De Silva S, Chea L, Nuon S, Saykao P, et al. Knowledge about hepatitis and previous exposure to hepatitis viruses in immigrants and refugees from the Mekong Region. Australian and New Zealand Journal of Public Health. 2005;29(1):64–8.

318. O'Connor C, Shaw M, Wen L, Quine S. Low knowledge and high infection rates of hepatitis in Vietnamese men in Sydney. International Journal of Sexual Health. 2008;5(3):299–302.

319. van der Veen Y, Voeten H, de Zwart O, Richardus J. Awareness, knowledge and self-reported test rates regarding Hepatitis B in Turkish-Dutch: a survey. BMC Public Health. 2010;10(1):512.

320. Wallace J, McNally S, Richmond J, Hajarizadeh B, Pitts M. Managing chronic hepatitis B: A qualitative study exploring the perspectives of people living with chronic hepatitis B in Australia. BMC Research Notes. 2011;4(1):45.

321. Kue J, Thorburn S. Hepatitis B knowledge, screening, and vaccination among Hmong Americans. Journal of Health Care for the Poor and Underserved. 2013;24(2):566–78.

322. Palmer C, Thomas M, von Wagner C, Raine R. Reasons for non-uptake and subsequent participation in the NHS Bowel Cancer Screening Programme: a qualitative study. British Journal of Cancer. 2014;110(7):1705–11.

323. Li D, Tang T, Patterson M, Ho M, Heathcote E, Shah H. The impact of hepatitis B knowledge and stigma on screening in Canadian Chinese persons. Canadian Journal of Gastroenterology. 2012;26(9):597–602.

324. Coronado G, Taylor V, Tu S, Yasui Y, Acorda E, Woodall E, et al. Correlates of hepatitis B testing among Chinese Americans. Journal of Community Health. 2007;32(6):379–90.

325. Nguyen T, McPhee S, Stewart S, Gildengorin G, Zhang L, Wong C, et al. Factors associated with hepatitis B testing among Vietnamese Americans. Journal of General Internal Medicine. 2010;25(7):694–700.

326. Taylor V, Bastani R, Burke N, Talbot J, Sos C, Liu Q, et al. Factors associated with hepatitis B testing among Cambodian American men and women. Journal of Immigrant and Minority Health. 2012;14(1):30–8.

327. Sweeney L, Owiti J, Beharry A, Bhui K, Gomes J, Foster G, et al. Informing the design of a national screening and treatment programme for chronic viral hepatitis in primary care : qualitative study of at-risk immigrant communities and healthcare professionals. BMC Health Services Research. 2015;15(97):1–17.

328. Mathur R, Bhaskaran K, Chaturvedi N, Leon D, Grundy E, Smeeth L. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. Journal of Public Health. 2014;36(4):684–92.

329. Mcmullen H, Griffiths C, Leber W, Greenhalgh T. Explaining high and low performers in complex intervention trials : a new model based on diffusion of innovations theory. Trials [Internet]. Trials; 2015;16(242). Available from: http://dx.doi.org/10.1186/s13063-015-0755-5

330. Greenhalgh T, Robert G, Macfarlane F, Bate P, Jyriakidou O. Diffusion of Innovations in service organizations: systematic review and recommendations. The Millbank Quaterly. 2004;82(4):581–629.

331. Veldhuijzen I, van Driel H, Vos D, De Zwart O, van Doornum G, De Man R, et al. Viral hepatitis in a multi-ethnic neighborhood in the Netherlands : results of a community-based study in a low prevalence country. International Journal of Infectious Diseases. 2009;13(1):9–13.

332. O'Leary M, Sarwar M, Hutchinson S, Weir A, Schofield J, Mcleod A, et al. The prevalence of hepatitis C virus among people of South Asian origin in Glasgow - results from a community based survey and laboratory surveillance. Travel Medicine and Infectious Disease. 2013;11(5):301–9.

333. Becares L. Which ethnic groups have the poorest health ? Ethnic health inequalities 1991 to 2011. 2013.

334. Hippisley-Cox J, Vinogradova Y. Trends in Consultation Rates in General Practice 1995 to 2008 : Analysis of the QResearch ®. 2009.

335. Govenment Equalities Office. Ethnic minority women's poverty and economic well being. 2010.

336. Williams R. Health and length of residence among South Asians in Glasgow : a study controlling for age. Journal of Public Health Medicine. 1993;15(1):52–60.

337. Mcdonald J, Kennedy S. Insights Into the " Healthy Immigrant Effect ": Health Status and Health Service Use of Immigrants to Canada Insights into the " healthy immigrant effect ": health status and health service use of immigrants to Canada. Social Sciences and Medicine. 2004;59:1613–27.

338. Patel S, Kai J, Avery A, Guo B, James M, Malins S et al. Clinical characteristics of persistent frequent attenders in primary care: case-control study. Family Practice. 2015;32(6):624-30

339. Webb R, Richardson J, Esmail A, Pickles A. Uptake for cervical screening by ethnicity and place-of-birth : a population-based cross-sectional study. Journal of Public Health (Bangkok). 2004;26(3):293–6.

340. Moser K, Patnick J, Beral V. Inequalities in reported use of breast and cervical screening in Great Britain : analysis of cross sectional survey data. British Medical Journal. 2009;338(b2025).

341. Renshaw C, Jack R, Dixon S, Møller H, Davies E. Estimating attendance for breast cancer screening in ethnic groups in London. BMC Public Health. 2010;10(157).

342. von Wagner C, Baio G, Raine R, Snowball J, Morris S, Atkin W, et al. Inequalities in participation in an organized national colorectal cancer screening programme : results from the first 26 million invitations in England. International Journal of Epidemiology. 2011;40:712–8.

343. Ward C, Cotzias T, Hargreaves S, Regan L, Foster G. Prevalence of hepatitis C among pregnant women attending an inner London obstetric department : uptake and acceptability of named antenatal testing. Gut. 2000;47:277–80.

344. Fernandez M, Manzanares S, Jacques C, Caylá J, Kunkel J, Foster G. Screening for chronic viral hepatitis in migrant populations Report on four HEPscreen pilot studies Screening for chronic viral hepatitis in migrant populations. 2014.

345. Senore C, Armaroli P, Silvani M, Andreoni B, Bisanti M, Marai L, et al. Comparing different strategies for colorectal cancer screening in Italy: predictors of patients' participation. American Journal of Gastroenterology. 2010;105(1):188–98.

346. Hewitson P, Ward A, Heneghan C, Halloran S, Mant D. Primary care endorsement letter and a patient leaflet to improve participation in colorectal cancer screening : results of a factorial randomised trial. British Journal of Cancer. 2011;105(4):475–80.

347. Wood DA, Kinmonth AL, Davies GA, Yarwood J, Thompson SG, Pyke SDM, et al. Randomised Controlled Trial Evaluating Cardiovascular Screening And Intervention In General Practice : Principal Results Of British Family Heart Study:Family Heart Study Group. British Medical Journal. 1994;308(6924):313–20.

348. Hellenius ML, Johansson J, de Faire U, Elofsson S, Krakau I. Four years experience of a cardiovascular opportunistic screening and prevention programme in the primary health care in Sollentuna, Sweden. Scandinavian Journal of Primary Health Care. 1999;17(2):111–5.

349. Lin S, Chang E, So S. Why We Should Routinely Screen Asian American Adults for Hepatitis B: A Cross-Sectional Study of Asians in California. Hepatology. 2007;46(4):1034–40.

350. Orkin C, Flanagan S, Wallis E, Ireland G, Dhairyawan R, Fox J, et al. Incorporating HIV / hepatitis B virus / hepatitis C virus combined testing into routine blood tests in nine UK Emergency Departments : the " Going Viral " campaign. HIV Medicine. 2016;17:222–30.

351. Harris R, Ramsay M, Hope V, Brant L, Hickman M, Foster G, et al. Hepatitis C prevalence in England remains low and varies by ethnicity : an updated evidence synthesis. European Journal of Public Health. 2012;22(2):187–92.

352. Denis F, Ranger-Rogez S, Alain S, Mounier M, Debrock C, Wagner A, et al. Sreening of pregnant women for hepatitis B markers in a French Provincial university hospital (Limoges) during 15 years. European Journal of Epidemiology. 2004;19(10):973–8.

353. Kim W. Epidemiology of Hepatitis B in the United States. Hepatology. 2009;49(2 (Suppl)):S28–34.

354. Baha W, Foullous A, Dersi N, They-they T, El alaoui K, Nourichafi N, et al. Prevalence and risk factors of hepatitis B and C virus infections among the general population and blood donors in Morocco. BMC Public Health. 2013;13(50).

355. Navarro N, Lim N, Kim J, Joo E, Che K, Runyon B, et al. Lower than expected hepatitis B virus infection prevalence among first generation Koreans in the U . S .: results of HBV screening in the Southern California Inland Empire. BMC Infectious Diseases. 2014;14(269).

356. Yuan J, Ross R, Stanczyk F, Govindarajan S, Gao Y, Hdenderson B, et al. A cohort study of serum testosterone and hepatocellular carcinoma in Shanghai, China. International Journal of Cancer. 1995;63(4):491–3.

357. Micallef J, Kaldor J, Dore G. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. Journal of Viral Hepatitis. 2006;13(1):34–41.

358. Lehmann M, Meyer M, Monazahian M, Tillmann H, Manns M, Wedemeyer H. High rate of spontaneous clearance of acute hepatitis C virus genotype 3 infection. Journal of Medical Virology. 2004;73(3):387–91.

359. Dalton A, Bottle A, Okoro C, Majeed A, Millett C. Uptake of the NHS Health Checks programme in a deprived , culturally diverse setting : cross-sectional study. Journal of Public Health. 2011;33(3):422–9.

360. Hughson J, Woodward-Kron R, Parker A, Hajek J, Bresin A, Knoch U, et al. A review of approaches to improve participation of culturally and linguistically diverse populations in clinical trials. Trials. 2016;17(263):1–10.

361. Jowett S, Macleod J, Wilson S, Hobbs F. Research in primary care : extent of involvement and perceived determinants among practitioners from one English region. British Journal of General Practice. 2000;50:387–9.

362. Royal College of General Practitioners. Patient safety implications of general practice workload. 2015.

363. White A, de Sousa B, de Visser R, Hogston R, Madsen S, Makara P, et al. The State of Men's Health in Europe Report. 2011.

364. Migration Advisory Committee. Migrants in low-skilled work. 2014.

365. Tarrant C, Wobi F, Angell E. Tackling health inequalities: socio-demographic data could play a bigger role. Family Practice. 2013;30:613–4.

366. Cummins C, Winter H, Cheng K, Maric R, Silcocks P, Varghese C. An assessment of the Nam Pehchan computer program for the identification of names of south Asian ethnic origin. Journal of Public Health Medicine. 1999;21(4):401–6.

367. Ryan R, Vernon S, Lawrence G, Wilson S. Use of name recognition software, census data and multiple imputation to predict missing data on ethnicity: application to cancer registry records. BMC Medical Informatics and Decision Making. 2012;12(3).

368. Segura J, Castells X, Casamitjana M, Macia F, Porta M, Katz S. A Randomized Controlled Trial Comparing Three Invitation Strategies in a Breast Cancer Screening Program. Preventative Medicine. 2001;33(4):325–32.

369. Everett T, Bryant A, Griffin M, Martin-Hirsch P, Forbes CA, Jepson RG. Interventions targeted at women to encourage the uptake of cervical screening. Cochrane Database of Systematic Reviews. 2011;5.

370. Fisher D, Hess K, Erlyana E, Reynolds G, Cummins C, Alonzo T. Comparison of Rapid Point-of-Care Tests for Detection of Antibodies to Hepatitis C Virus. Open Forum Infectious Diseases. 2015;2(3):1–6.

371. Khuroo MS, Khuroo N, Khuroo MS. Diagnostic accuracy of point-of-care tests for hepatitis C virus infection: a systematic review and meta-analysis. PLoS One. 2015;10(3):1–22.

372. Khuroo MS, Khuroo N, Khuroo MS. Accuracy of rapid point-of-care diagnostic tests for hepatitis B surface antigen-a systematic review and meta-analysis. Journal of Clinical and Experimental Hepatology. 2014;4(3):226–40.

373. Bottero J, Boyd A, Gozlan J, Lemoine M, Carrat F, Collignon A, et al. Performance of rapid tests for detection of HBsAg and anti-HBsAb in a large cohort, France. Journal of Hepatology. 2013;58(3):473–8.

374. Njai H, Shimakawa Y, Sanneh B, Ferguson L, Ndow G, Mendy M, et al. Validation of rapid point-of-care (POC) tests for detection of hepatitis B surface antigen in field and laboratory Settings in the Gambia, Western Africa. Journal of Clinical Microbiology. 2015;53(4):1156–63.

375. Macpherson P, Chawla A, Jones K, Coffey E, Spaine V, Harrison I, et al. Feasibility and acceptability of point of care HIV testing in community outreach and GUM drop-in services in the North West of England : a programmatic evaluation. BMC Public Health. 2011;11(419).

376. Turner P, Van Den Bruel A, Jones C, Plüddemann A, Heneghan C, Thompson M, et al. Point-of-care testing in UK primary care : a survey to establish clinical needs. Family Practice. 2016;1–7.

377. Leber W, McMullen H, Anderson J, Marlin N, Santos A, Bremner S, et al. Promotion of rapid testing for HIV in primary care (RHIVA2): a cluster-randomised controlled trial. Lancet HIV. 2015;2(6):e229-235.

378. Mohamed S, Raimondo A, Penaranda G, Camus C, Ouzan D, Ravet S, et al. Dried Blood Spot Sampling for Hepatitis B Virus Serology and Molecular Testing. PLoS One. 2013;8(4).

379. Greenman J, Roberts T, Cohn J, Messac L. Dried blood spot in the genotyping , quantification and storage of HCV RNA : a systematic literature review. Journal of Viral Hepatitis. 2015;22(4):353–61.

380. Campbell M, Grimshaw J. Cluster randomised trials: time for improvement. British Medical Journal. 1998;317(7167):1171–2.

381. Dore G, Ward J, Thursz M. Hepatitis C disease burden and strategies to manage the burden. Journal of Viral Hepatitis. 2014;21(S1):1–4.

382. Moorman A, Xing J, Ko S, Rupp L, Xu F, Gordon S, et al. Late diagnosis of hepatitis C virus infection in the Chronic Hepatitis Cohort Study (CHeCS): Missed opportunities for intervention. Hepatology. 2015;61(5):1479–84.

383. Bernstein D, Kleinman L, Barker C, Revicki D, Green J. Relationship of Health-Related Quality of Life to Treatment Adherence and Sustained Response in Chronic Hepatitis C Patients. Hepatology. 2002;35(3):704–8.

384. Hassoun Z, Willems B, Deslauriers J, Nguyen B, Huet P. Assessment of Fatigue in Patients with Chronic Hepatitis C Using the Fatigue Impact Scale. Digestive Diseases and Sciences. 2002;47(12):2674–81.

385. Coughlan B, Sheehan J, Hickey A, Crowe J. Psychological well-being and quality of life in women with an iatrogenic hepatitis C virus infection. British Journal of Health Psychology. 2002;7(1):105–16.

386. Wessely S, Pariante C. Fatigue, depression and chronic hepatitis C infection. Psychological Medicine. 2002;32:1–10.

387. Cordoba J, Reyes J, Esteban J, Hernandez J. Labeling may be an important cause of reduced quality of life in chronic hepatitis C. American Journal of Gastroenterology. 2003;98(1):226–7.

388. Gill M, Atiq M, Sattar S, Khokhar N. Psychological implications of hepatitis C virus diagnosis. Journal of Gastroenterology and Hepatology. 2005;20(11):1741–4.

389. Golden J, Conroy R, O'Dwyer A, Golden D, Hardouin J. Illness-related stigma , mood and adjustment to illness in persons with hepatitis C. Social Sciences and Medicine. 2006;63(12):3188–98.

390. Singh G, Miller B. Health, life expectancy, and mortality patterns among immigrant populations in the United States. Canadian Journal of Public Health. 2004;95(3):14–20.

391. Harding S. Mortality of migrants from the Indian subcontinent to England and Wales: effect of duration of residence. Epidemiology. 2003;14(3):287–92.

392. Norredam M, Nielsen S, Krasnik A. Migrants ' utilization of somatic healthcare services in Europe — a systematic review. European Journal of Public Health. 2009;20(5):555–63.

393. Mcgee H, Hickey A, Byrne M. Review of health services available for persons who contracted hepatitis C through the administration within the state of blood or blood products. 2000.

394. Sewitch M, Abrahamowicz M, Bitton A, Daly D, Wild G, Cohen A, et al. Psychological distress, social support, and disease activity in patients with inflammatory bowel disease. American Journal of Gastroenterology. 2001;96(5):1470–9.

395. Guthrie E, Jackson J, Shaffer J, Thompson D, Tomenson B, Creed F. Psychological disorder and severity of inflammatory bowel disease predict health-related quality of life in ulcerative colitis and Crohn's disease. American Journal of Gastroenterology. 2002;97(8):1994–9.

396. Hameed K, Gibson T. A comparison of the prevalence of rheumatoid arthritis and other rheumatic diseases amongst Pakistanis living in England and Pakistan. British Journal of Rheumatology. 1997;36(7):781–5.

397. Allison T, Symmons D, Brammah T, Haynes P, Rogers A, Roxby M, et al. Musculoskeletal pain is more generalised among people from ethnic minorities than among white people in Greater Manchester. Annals ofthe Rheumatic Diseases. 2002;61(2):151–6.

398. Njobvu P, Hunt I, Pope D, Macfarlane G. Pain amongst ethnic minority groups of South Asian origin in the United Kingdom : a review. Rheumatology. 1999;38(12):1184–7.

399. May L. A report into attitudes towards mental health problems in the South Asian community in Harrow, North London. 2010.

400. Gray J, Majeed A, Kerry S, Rowlands G, Gray J. Identifying patients with ischaemic heart disease in general practice: cross sectional study of paper and computerised medical records. British Medical Journal. 2000;321(7260):548–50.

401. Edwards T, Stern A, Clarke D, Ivbijaro G, Kasney L. The treatment of patients with medically unexplained symptoms in primary care : a review of the literature. Mental Health and Family Medicine. 2010;7(4):209–22.

402. Gearing R, Mian I, Barber J, Ickowicz A. A methodology for conducting retrospective chart review research in child and adolescent psychiatry. Journal of the Canadian Acadamyof Child and Adolescent Psychiatry. 2006;15(3):126–34.

403. NHS digital. GP2GP [Internet]. 2017 [cited 2017 Jan 27]. Available from: https://digital.nhs.uk/gp2gp

404. Lapointe L, Ramaprasad J, Vedel I. Creating health awareness: a social media enabled collaboration. Health and Technology. (2014) 4: 43.doi:10.1007/s12553-013-0068-1

Appendices

Appendix 1: The HepFree trial protocol version 7.0

TITLE OF THE PROTOCOL:

Chronic Viral Hepatitis in First and Second Generation Immigrants from 'At Risk' Countries. A controlled randomised cross sectional cluster trial to assess the impact of identifying, screening and treating immigrants with viral hepatitis.

Short title/Acronym:	HepFree
Sponsor:	Queen Mary University of London Representative of the Sponsor: Gerry Leonard Head of Research Resources Joint Research Management Office Queen Mary Innovation Centre 5 Walden Street London E1 2EF Phone: 020 7882 7260 Email: sponsorsrep@bartshealth.nhs.uk
REC reference:	12/LO/1768

Chief Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 7.0, dated 12th March 2015)**,or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name:

Chief Investigator Site:

Signature and Date:

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 7.0, dated 12th March 2015)**,or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

STUDY SUMMARY/SYNOPSIS

TITLE	Chronic viral hepatitis in first and second generation immigrants from 'at risk' countries. A controlled randomised cross sectional cluster trial to assess the impact of identifying, screening and treating immigrants with viral hepatitis.
SHORT TITLE	HepFree
Protocol Version Number and Date	7.0 dated 12th March 2015
Methodology	A controlled randomised cross sectional cluster trial to determine how to effectively identify and screen immigrants from 'at risk' ethnic minority communities as well as assessing the impact of primary care on engagement of targeted newly diagnosed chronic viral hepatitis patients.
Study Duration	5 years
Study Centre	There will be 56 centres to be utilised over old Primary care trusts (including Bradford as well as South and East London), known to have a high density of immigrant populations from 'at risk' countries (WHO classification of HBV prevalence >2%)
Objectives	**Primary objectives** • To assess the most cost effective method of screening for chronic viral hepatitis in primary care patients within 'at risk' ethnic minority communities. • To assess the impact of the interventional approach based

strategy to screening.

- To establish whether the involvement of community therapy is likely to have an impact on a patient's engagement after having been positively tested for viral hepatitis.

- To assess differences in treatment adherence between patients groups receiving treatment within the community against those who have standard hospital care.

Number of Subjects/Patients

- It is postulated that up to 48,000 prospective patients could be approached to be screened, with demographic data from the control practices to be provided for another prospective 4,000 patients.

- Up to 3500 of these prospective patients will be contacted prior to screening by their GP, to try and collect baseline information relating to explanatory models of viral hepatitis as well as demographics and other contextual variables that relate to screening uptake and subsequent treatment engagement, using 2 different questionnaires.

- Estimates indicate that up to approximately 19,200 will screened with 3% testing positive for viral hepatitis.

- Up to approximately 580 infected patients will likely be used to assess the impact of community care or standard hospital care for patient engagement.

Main Inclusion Criteria

- Female and male patients who have been identified as first generation immigrants born in a country of high risk or second generation immigrants. Please see appendix 2 – for the complete listing of countries that deemed high risk (as outlined by WHO classification of HBV prevalence >2%).

- >18 years of age.

Statistical Methodology and Analysis

For this clustered trial, it is assumed an intra-cluster correlation co-efficient of 0.05 for all outcomes and a coefficient of variation of cluster size of 0.65.

We are making three comparisons in this two-stage trial:

Stage 1

Comparison A: Control vs Interventional screening practices gives >80% power to detect a difference from 15% to 40% in testing rates at 5% significance level).

Comparison B: Standard invitation vs enhanced invitation gives 88% power to detect a difference from 32% to 42% in testing rates at 5% significance level).

Stage 2

Comparison C: Standard hospital treatment vs treatment in community gives 90% power to detect a difference from 50% to 70% in engagement rates assuming 40% of eligible patients will be screened and 3% test positive).

Analyses will use appropriate methods to take account of clustering. Because of the nature of the outcomes we anticipate few missing values so that generalised estimating equations should produce unbiased results. For comparison A we will also conduct a cluster-level analysis as a sensitivity analysis because of the imbalance in the number of clusters per arm.

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
HRA	Health Research Authority
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
JRMO	Joint Research Management Office
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control

Participant	An individual who takes part in a clinical trial
PCTU	Pragmatic Clinical Trials Unit
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

Index **Page Number**

1. Introduction

1.1 Background

Chronic viral hepatitis is common in people born outside the UK and involves persistent infection with either hepatitis B or hepatitis C virus. The disease can cause asymptomatic disease that leads to cirrhosis or potentially hepatocellular carcinoma as well as death in a large proportion of those who are infected.

Hepatitis C virus is a blood borne single strand RNA virus which exists in a number of different genotypes. Chronic infection (defined as infection for more than 6 months) is usually asymptomatic and patients usually remain unaware that they are infected until the disease has progressed. However, disease progression and severity is highly likely.

Hepatitis B is a blood borne DNA virus that may also be transmitted sexually or by materno-fetal transmission. Chronic HBV is defined by the presence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection. The disease persists in a number of different, convertible phases. The two major phases are defined by the presence or absence of the hepatitis B e antigen (HBeAg) in the circulation.

These often asymptomatic diseases require multifaceted diagnostic testing, which includes serial testing for antibodies, RNA/DNA as well as liver function tests to ensure patients are accurately diagnosed.

The prevalence rate of viral hepatitis currently stands at approximately 0.5% within the UK. However, statistics for first and second generation immigrants from 'at risk' countries indicates a higher prevalence, perhaps approaching 5%. Current data relating to immigrant populations within the UK is limited. However, it is believed that 7 million first and second generation immigrants from high prevalence countries currently reside in the UK. It is believed that certain 'at risk' communities have a prevalence level similar to their country of origin, as demonstrated by studies conducted in the Somali community in Liverpool as well as the Pakistani community in London, (Brabin *et al*., 2002 and Uddin *et al*., 2010). Hence the

prevalence of viral hepatitis is at least ten fold greater in immigrants than in the indigenous community.

The UK has one of the lowest rates of therapy for viral hepatitis in Europe and this is undoubtedly contributing to the observed rising mortality from liver disease in the UK. This is, in contradistinction to the rest of Europe, where mortality from liver disease is decreasing. Previous UK studies have shown that access to therapy for patients known to have viral hepatitis is poor with only a tiny minority of diagnosed patients going on to receive treatment.

Current statistics indicate that of the total UK population that have been infected with hepatitis C, only 17% have been diagnosed and less than 2% go on to receive treatment (Ryder., S, 2004). Hepatitis B is known to be the cause of 50% of primary liver cancer cases within the UK, in which patients are 100 times more likely to develop hepatocellular carcinoma than those who are not infected. Strategies culminating in improved access to treatment are thought likely to have a major impact on treatment uptake and to reduce morbidity. However, currently alternatives to hospital based treatment have not been studied.

Current data indicates that approximately 25% of those with chronic viral hepatitis will die in their fifth decade as a result of their infection, indicating that up to 50,000 immigrants living in the UK may develop cirrhosis and/or liver cancer. The subsequent care of patients with these conditions will add a significant financial burden to the NHS. Further analysis of the current demographics of the immigrant population shows that over 80% are less than 50 years old (Foster, G – unpublished data). It is therefore anticipated that there will be a sharp rise in the number of immigrant deaths associated with viral hepatitis over the coming decade.

Therapy for chronic viral hepatitis is available and is clinically and cost effective as indicated by NICE approval. For chronic HCV infection therapy involves a combination of a long acting interferon combined with ribavirin and, increasingly a direct acting antiviral agent (such as telaprevir or boceprevir). For chronic HBV infection a number of different treatment options are available including interferon based immunomodulatory regimes or perpetual viral suppression with a third generation nucleotide derived antiviral agent, either entecavir or

tenofovir. The current model of care involves specialist centres with highly trained staff administering therapy at some distance from the patient's home.

Given the poor uptake of antiviral therapy under current conditions it has been suggested that alternative treatment models should be developed but these have not been assessed or tested in a large scale.

2.Trial Objectives and Design

2.1 Trial Objectives

The central objective of the study is to determine whether screening for chronic viral hepatitis in immigrants living in the UK by testing all registered immigrants in GP surgeries is feasible, effective, and cost effective.

We will examine the costs and benefits of screening compared to current 'standard practice' and evaluate whether an enhanced patient information invitation letter (as opposed to 'standard patient information invitation letter') enhances engagement as well as determining whether local delivery of therapy improves engagement when compared to conventional delivery of care.

Prior to the commencement of screening, we will also look at the contextual variables and health literacy that will have an impact and influence the uptake of screening and subsequent engagement in treatment. This will be done with a population-based survey of knowledge of viral hepatitis in conjunction with other questionnaires, Patient Health Questionnaire [PHQ-9] and Generalised Anxiety Disorder 7-item [GAD-7] . The survey questionnaire is to determine the range and prevalence of different beliefs, attitudes and barriers to screening.

The specific study objectives are listed below:

Primary Objectives

Stage 1

- To determine whether interventional screening is more cost-effective than control screening in the detection of viral hepatitis in ethnic minority patients in primary care.

To determine whether the provision of an enhanced patient information invitation letters increases attendance for testing when compared to standard information invitation letter.

Stage 2

- To determine whether community based therapy is superior to conventional delivery of treatment (based on referral to local hospital treatment centres) as measured by engagement with management.

Secondary Objectives

- To determine the range and prevalence of different beliefs, attitudes and barriers to screening.
- To assess the impact of contextual variables and demographics as well as health literacy in the uptake rate of screening and subsequent treatment engagement.
- To assess treatment adherence between patient groups receiving treatment within the community care setting against standard hospital care.
- To determine the cost effectiveness of the interventions
- To determine the prevalence of viral hepatitis in different ethnic groups living in the UK

Primary Endpoint

- The proportion of patients eligible to be screened (determined by a review of the number of immigrants registered at the GP practice at the initiation of the study)
- The proportion of potential participants that attend for testing
- The proportion of potential participants that engage in therapy in the different treatment arms. Engagement is defined as:
    - Attending at least 3 different occasions
    - For patients who are HCV antibody positive or equivocal but HCV RNA negative attending the GP practice or the local hospital on two separate occasions.

Secondary Endpoint

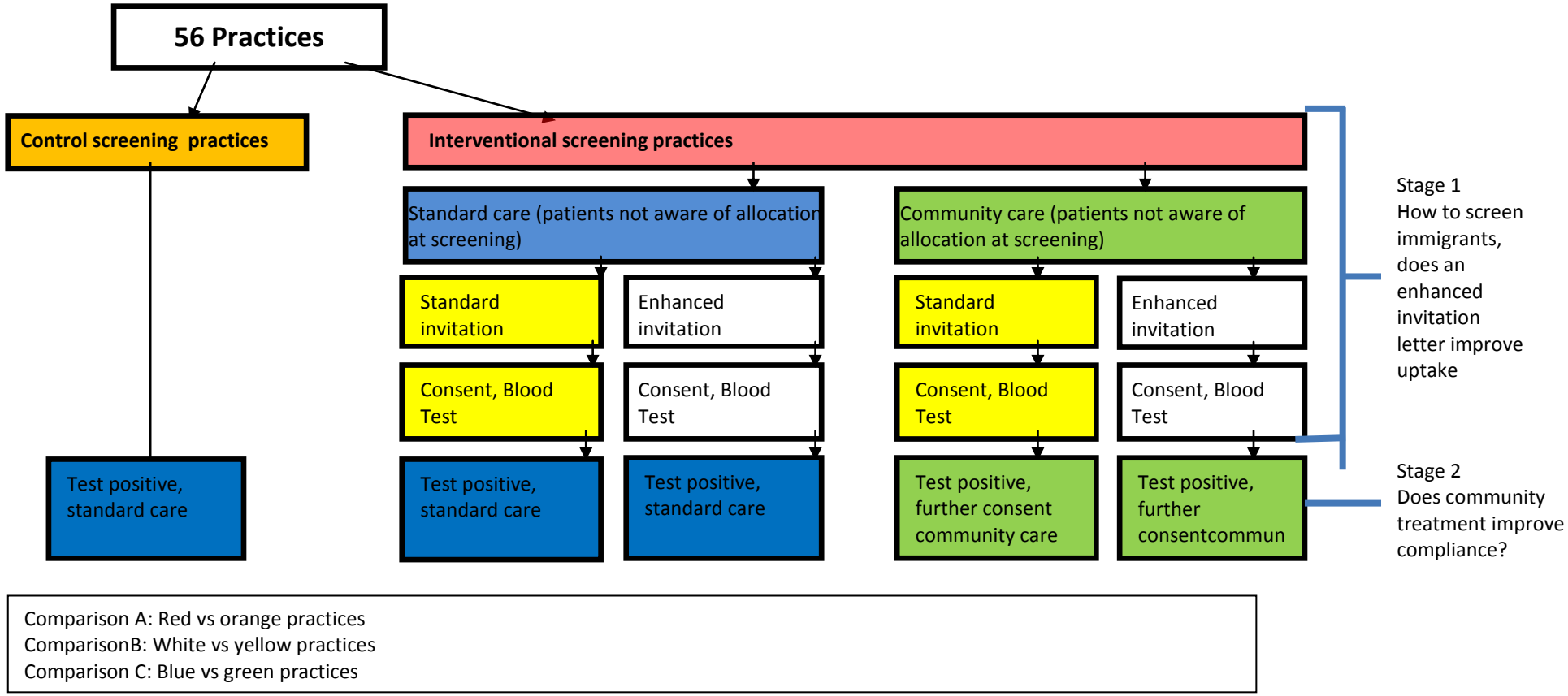
- Adherence will be measured upon 80% completion of prescribed therapy, as confirmed at 12 month follow up. However, if the participant is under active monitoring, adherence will be measured by their level of engagement as defined above.

2.2 Trial Design

It is a two stage cluster randomised trial. The first stage (two arms) determines how to effectively identify and screen immigrants from 'at risk' ethnic minority communities for chronic viral hepatitis. Within the first stage of the trial we will determine whether or not patients who receive an enhanced patient information invitation letter agree to participate in testing at the same rate as patients who receive a standard patient information invitation letter.

The second stage (two arms) investigates if treatment in primary care (community based therapy) impacts on the engagement of follow up and treatment. There will be an in-depth investigation into a small subset of these participants to assess impact of contextual variables and demographics as well as health literacy in the uptake rate of screening and subsequent treatment engagement.

2.3 Main Study Scheme Diagram



Comparison A: Red vs orange practices
ComparisonB: White vs yellow practices
Comparison C: Blue vs green practices

3. Subject Selection

3.1 Number of Subjects and Subject Selection

Stage 1

Up to 48,000 prospective patients from known ethnic minority populations will be contacted (interventional screening). First and second generation immigrants from known 'at risk' communities (as detailed in appendix 2) will be identified utilising GP practice list definitions of ethnicity.

Prior to the commencement of screening, up to 8 'intervention' GP practices will be involved in generating a representative random sample identified by ethnicity group. The sample will reflect the wider population of those that are potentially eligible for screening. Up to 3500 of the pool of potential participants will be contacted to take part in the pre-screening survey component.

Potential participants from GP practices employing interventional screening will be approached in a number of different methods in accordance with local clinical practice. Patients will be contacted either by letter, text message or opportunistically when visiting the GP. In all circumstances the patient will be given time to consider whether or not they wish to participate and patients may choose to re-attend the practice at a later date to confirm participation. Written Informed Consent will be taken from the patient prior to commencement of the screening process. Patients will then be tested using standard local testing approaches – in practices with on-site phlebotomy we will use local phlebotomy and for practices that refer patients for blood testing the usual referral policy will be followed. Once the results are available, the patient will be contacted. If tested positive for viral hepatitis, the patient will be invited to re-attend the GP practice to receive their result and patients will then be offered appropriate therapy. At this stage patients who have tested positive for infection will be offered the choice of continuing with standard management (i.e. treatment within hospital) or taking part in Stage 2 of the study in which standard

management is compared with community care (see section 4.1.3 for full detail of the invitation and consent procedures)

Immigrant demographics from control GP practices for a further 4,000 potential participants will be monitored with regards to testing for viral hepatitis and how many engage with regards to subsequent treatment. This will be fully anonymised prior to data being exported and sent to the data management team for data collection.

Screening and treatment of the identified patients will last for 2 - 3 years with a staggered approach to GP site initiations to ensure a consistent flow of patients.

Stage 2

GP practices employing interventional screening will be randomised into two different arms, hospital treatment (standard care) or community care treatment. In GP practices that are randomised to the hospital treatment arm, participants that are found to be positive for viral hepatitis will be treated at their local hospital, as per standard care. In GP practices randomised to the community care arm, participants that are found to be viral hepatitis positive will be treated for viral hepatitis in a local GP practice by a member of the clinical hepatology team.

3.2 Inclusion Criteria

Stage 1

- > 18 years old
- First and Second Generation immigrants of appropriate ethnicity (born or born to parents that originate from a country of high prevalence (Please see Appendix 2 for comprehensive list of countries listed by WHO as >2% HBV prevalence)

Stage 2

- Inclusion is as for Stage 1 , with the additional criteria:
- Patient who test positive for viral hepatitis during screening

3.3 Exclusion Criteria

Stage 1

- <18 years old
- Lacking capacity

Stage 2

- Exclusion is as for Stage 1 , with the additional exclusion criteria:
- Patients that screen negative for viral hepatitis

3.4 Premature withdrawal

Withdrawal of informed consent.

Data up to the point of withdrawal will be retained and used in the analysis.

4. Study Procedures

4.1 Informed Consent Procedures

4.1.1 Consent for the Pre-screening Component (Survey)

For the subset of participants to be approached for this survey completion, it is proposed that verbal consent be sought. The fundamental principles that underlie both verbal and written consent are, in essence, the same. The main issue surrounds informing the potential participant as to the nature of the research, their rights and safety as participants and making explicit that participation is voluntarily and can be revoked at any time without reprisal. From our previous work, we discovered that ethnic minorities were often willing to participate but concerned about signing anything, perhaps if there literacy problems or concerns about 'authorities' not acting in their interest which is common amongst refugees, for example, or recent migrant who may be settling into a new life.

There is an element of culturally sensitivity that should be observed within this potential participant-population as many will see the signing of forms as an official act with subsequent retributions in the future. This may be seen as having negative connotations, bringing about considerable scepticism relating to participation. Verbal consent may be deemed as a less threatening act. It is known that there is incidence of illiteracy and semi-illiteracy in this particular population demographic.

The main concerns are to not discriminate against participation by using a methodology that reduced their chances of participation because of language or cultural factors, or issues related to social exclusion; for example, postal addresses may chance if the population are mobile, or shared accommodation, or loss of post may be factors in non-response.

HRA guidance 'Consent& Participation Information Sheet Preparation Guidance' released on March 3rd 2014, details that participants can give 'written, oral or non-verbal' consent. The objective is to ensure that the patient's decision is recorded and that discussions that surround this decision

It is likely that the vast majority of the interviews are likely to be conducted via telephone as to create minimal intrusion or disruption on account of participation, written consent may not be seen as the most practical route of obtaining consent. However, it will be made explicit that the consent can be withdrawn at any point during the course of the interview. This methodology has been tested previously and worked successfully with ethnic groups in primary care.

As detailed by NRES Guidance, Annex 5: Consent and its problems – the stipulation of written informed consent could be act as a barrier to recruitment, particularly when there is an imperative need to obtain a representative sample, with the potential benefit deemed significant.

The intended mechanism, as discussed with the sponsor, is to use patient information letter and using the HRA template consent form as a means of obtaining informed verbal consent,

at minimum at the start and the end of the interview. The participant will be allowed to ask any further questions to ensure that they have understood what is involved and their participation is voluntary, and can be withdrawn at any time. This demonstrates that consent an ongoing process and not a one off event. If required, it will be repeated and enforced during the course of the interview. Although, in the first instance, the crucial time points are at the commencement of the interview and at the end. This process has been discussed with the sponsor, and they have indicated their approval for the research team to proceed.

In each instance, verbal consent will be taken in the presence of an independent witness and adequately documented. A similar methodology has been used in previous studies of East London immigrants, within a survey in primary care of different ethnic groups (Rudell, K. *et al*., 2009).

4.1.2 Consent for Stage 1 of the Trial

Stage 1 of the trial is investigating two different methods of screening, i.e targeted screening which takes place at intervention practices or current standard practice at control practices.

4.1.2.1 Consent for the Screening at Intervention Practices

In the intervention practices, it is the responsibility of the investigator, or a person delegated this task by the investigator, to obtain written informed consent from each subject to the testing and data collection for further analyses (specifically they will be asked if they agree to allow the HepFree trial team to access their medical records and for data held by The Health and Social Care Information Centre to be made available to the research team. The investigator will adequately explain the aims, methods, anticipated benefits, and potential hazards of these procedures. In the case where the patient is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the subjects are completely free to not to be tested or to withdraw consent for data collection at any time. If participants do not wish to allow certain aspects of their data to be collected this can be indicated in the consent form.

They will still be able to enter the study but in this case only anonymised aggregate data will be collected for analysis.

4.1.2.2 Consent for Screening at Control Practices

In control GP practices, fully anonymised demographic data will be collected, with no patient identifiable information being collected or viewed outside the direct healthcare team. Information collected will be the number of individuals registered at the practice from each minority group, the number of these individuals that have been tested for viral hepatitis, the number of which tested positive, the number of individuals that engaged in their therapy. This is in line with Department of Health's Advisory Group on Hepatitis, recommending systematic case finding in primary care for chronic HBV/HCV infected individuals from minority ethnic populations that are born in countries that have intermediate to high prevalence of HBV infection. If testing positive, there should be contact tracing of close contacts including family members whilst infected individuals will be managed as per standard clinical care.

We are hoping to establish a true and accurate indication of viral hepatitis screening and engagement rates in communities of high risk immigrants. Individual participant informed consent will not be sought as it would add a source of contamination bias to the true patient screening and engagement rates. This could compromise the scientific integrity of the study if this has an impact on their behaviour.

However, no personal or patient identifiable information will be required – all data will be fully anonymised and only demographic numbers (as detailed above) will be used as data for the study in relation to the control cluster of GP practices.

Patients that test for viral hepatitis in control practices will be counselled by their doctors about chronic viral hepatitis (standard medical practice) and they will give verbal consent to for this test. Hence there will be minimal differences between the control group and the intervention group.

4.1.3 Consent for Stage 2 of the trial

Patients eligible for stage 2 of the trial (testing positive for viral hepatitis in the screening intervention practices) will be invited to participate by a member of the clinical hepatology team. A patient information sheet will provide a comprehensive account of the treatment/monitoring phase (stage 2) of the trial enabling the participant to make an informed decision as to whether they would like to remain on the trial or not. The patient information sheet will not indicate whether the patient's GP practice was randomised to standard care (care in hospital as per standard practice) or intervention (care at a local community care practice) arm. The investigator, or delegated member of the HepFree team, consenting the eligible patients will not be aware of the patient's allocation at the time when consent is sought (see section 4.2.4). Participants that consent to take part in this second trial, will subsequently be informed of their treatment/monitoring allocation by the doctor or health care practitioner who will manage their treatment. Participants that do not wish to take part in the second stage of the trial will be treated as per standard care. Treatment allocation will be concealed until after consent to participate in the trial has been obtained, in an effort to prevent bias between recruitment into the two arms of the trial (community vs hospital care). Patients will be explicitly informed of their right to withdraw from the study if they are not comfortable with their treatment allocation at any point. If a participant subsequently withdraws consent to the trial they will be treated as per standard of care (see section above).

4.2 Study Procedure Overview

56 GP practices across East London, South London and Bradford will be invited to participate within this study. Practice selection will be based on an established patient population of first and second generation immigrants from 'at risk' countries. The GP practices will either be allocated to one of the following five groups:

A) Control screening practices
B) Intervention screening practices with standard hospital treatment, standard invitation
C) Intervention screening practices with standard hospital treatment, enhanced invitation
D) Intervention screening practices with community care to be offered, standard invitation
E) Intervention screening practices with community care to be offered, enhanced invitation

In the first stage of the trial to assess screening methods we will compare group A with all the others combined.

In the second stage trial to assess treatment options we will compare groups B & C with groups D & E

In a supplementary analysis to assess the enhanced invitation we will compare groups B & D with groups C & E

4.2.1 Pre-screening Component (survey)

A small subset of up to 3500 potential participants from up to 8 of targeted screening practices, form the sample for a population based survey of those eligible for screening, in order to assess characteristics of take or decline, at all stages of the project.

The patients will be asked about their illness perceptions and narratives (called explanatory models) about hepatitis using an adapted version of the Barts Explanatory Model Interview checklists. These have been developed from focus groups and literature review information, following the methods set out in the original development for use in common mental disorders. Three other validated patient-reported outcomes will be completed by interview: patient health questionnaire (PHQ-9) and the generalized anxiety disorder 7-item (GAD-7) scale.

Some information about the individual will be available from primary care electronic databases, that will help establish the need for translated material or not. Potential participants will be contacted by a letter of invitation to participate within the survey, with further information detailing the project (in English or appropriate translation).

The letter would detail what is involved and that agreement or not to complete questionnaires is completely voluntary. In the first instance, telephone interviews will be the primary choice used for completion. However, the invitation letter will detail and accommodate if the participant prefers to receive an interview face to face, or if they prefer a postal survey. The letter will also indicate that contact after 2 weeks will be made to ascertain if they would be willing to participate.

After 2 weeks, potential participants will be contacted from the GP practice, via telephone (up to 3 times) to confirm if they received the letter and If they have any questions for the GP or the research team, indicating that they are happy to continue and participate.

If the participant indicates that they are willing to be interviewed over the phone, verbal consent in the presence of a witness will be sought with appropriate language translation (as required) and documented. It will be highlighted that participation is voluntary and the interview can be stopped at any time, if they do not wish to continue. The interview will be concluded with a documented verbal consent.

If the participant details that they would prefer to complete the surveys via post, all documents with instructions will be forwarded with a self-addressed envelope with a contact telephone number for any enquiries. If, the participant details that they would prefer face to face interview, a suitable time will be arranged with appropriate language translation (as required) to attend the GP practice.

4.2.2 Screening in Control GP Practices

In the control group arm, existing GP registers of patients will be screened to identify patients that fit the HepFree eligibility criteria, by their country of birth or their parents' country of birth. In conjunction with this, a local hepatologist or a trained member of the study team will

visit the GP practices, highlighting the study to the GPs and their teams and educating them about hepatitis B and C. These practices will continue with their standard care policy relating to screening over the 12 – 18 months of screening.

4.2.3 Screening at Intervention Practices

In the intervention practices, existing GP registers of patients will be screened to identify eligible patients by recorded ethnicity, country of birth or their parents' country of birth and first language spoken. Potential participants identified as first or second generation immigrants without HBV or HCV status, will either be contacted or approached to take part in the trial .

Potential participants for screening will be invited by their GP practices to have a blood test for viral hepatitis. The GP, or delegated and trained members of staff, will provide a copy of the patient information sheet and informed consent form (in English or appropriate translation, if applicable). This will explain the details of the study relating to screening and if they test positive for viral hepatitis.

After up to 4 weeks, participants that have been sent an invitation letter may be contacted to ensure receipt of the letter. If they wish to attend, an appointment will be made. Alternatively, participants can also contact or attend their GP to discuss further and decide whether to be tested.

Approximately 48,000 'targeted' patients from 'at risk' countries will be approached over a maximum18month period. All those screened and tested positive for viral hepatitis will either be offered treatment in the specialist out patients clinic in their local hospital or in an 'intervention practice' as part of community care. The location of where patients receive their treatment will be dependent on the interventional cluster allocation.

During the screening period, a hepatitis awareness campaign will be set up and conducted by a local community group within East London during the screening period. It will involve a series of awareness videos to be broadcast on local immigrant channel/ stations as well as

producing awareness posters to be displayed in local community centres to try and raise awareness and local knowledge about Hepatitis B and C. The impact of this awareness campaign will be assessed by looking at screening uptake rates of the practices within the area. This awareness campaign will also be fed into the cost benefit analysis of screening.

4.2.4 Participants with Chronic Viral Hepatitis

Participants who test positive for viral hepatitis, and consent to remain on the study, will receive treatment/monitoring in the specialist out patients clinic in their local hospital or in alocal community care practiceas part of community care. The treatment option for each patient will depend on the allocation of their practice, whether to the treatment intervention (local community care practice) or control arm (standard hospital). To reduce the chance of bias between the two arms, consent to be part of the second stage trial will be sought for both arms in the same way, by a member of the direct clinical care team, who, ideally, will be blinded to allocation. The status of the person seeking consent will be documented. Consent will be sought on the participant's first visit to see the clinical hepatology team, after receiving their positive result for viral hepatitis. If the participant consents to remain on the study, they will be unblinded to their treatment allocation.

Patients who test positive for viral hepatitis will be monitored for their level of engagement as well as treatment adherence as a secondary study outcome. Engagement will be measured relating to the patient's attendance and we will define 'engaged' as:

- Attending three visits after receiving a viral hepatitis positive result over the first 12 months
- OR
- For patients who are HCV antibody positive or equivocal but HCV RNA negative attending the GP practice or the local hospital on two separate occasions

This will allow an assessment of engagement in patients who do not wish to receive or are not suitable for antiviral therapy at this time. Attendance at 12 month follow up will be captured to ascertain if the patient was engaged and adhered to their care and treatment. Patients who undergo therapy will be assessed for adherence by treatment compliance - taking more than 80% of the prescribed medication.

Patients will either receive their standard local hospital care upon referral from the designated practices, in which case local consultant physicians will manage their treatment and monitoring in line with current practice. In 'community care' practices, patients who agree to undergo therapy in the community will be asked to attend a designated GP practice where a specialist viral hepatitis nurse and/or hepatologist will attend and deliver care in the community in accordance with a community treatment algorithm established and supervised by the local secondary care centre (see section 4.4).

4.3 Screening/Randomisation Procedure

Each GP practice will be randomised to one of the five arms at the outset. See section 4.2 for detail. Randomisation is undertaken by the Pragmatic Clinical Trials Unit.56 Practices are to be stratified by region in conjunction to be minimised by the number of eligible patients.

4.4 Schedule of Treatment

Standard therapy for chronic viral hepatitis will be provided as described in Section 4.2.4

Treatment and any related decisions will be overseen by a named local specialist

consultant, with GP input and nurse management, in line with usual standard of care.

4.5 Schedule of Assessment

Patients who fit the eligibility criteria will be invited to attend for hepatitis B and C screening. If an eligible patient attends their GP practice during the HepFree screening period, they may be opportunistically offered hepatitis B and C screening, providing informed consent is sought. Once written informed consent is in place, the patient will provide a blood sample for testing, following local phlebotomy services and provisions. The patient will be re-contacted to receive the test results. To meet the primary objectives of this study the viral hepatitis screening outcome will be collected by the research team and this data will be provided to the research team in an anonymised format, linked only to an anonymised identifier. Thus the participant's identity could not be deduced from the HepFree database. The identity of the

participant will not be known to anyone outside the direct clinical care of the participant, or members of the virology team, as per standard practice.

Patients, who test positive will be contacted, to visit their practice to receive their result. If unsuccessful, these patients will be recorded as being 'non-attenders'

If the patient tests positive, the patient will be treated at either their local hospital specialist centre or stay in community care under supervision of the hepatology consultant and nurse at the 'community care practices'. On a regular basis, a member of the team will conduct review of specific referral forms or accesses the patient's electronic records via CRS/PAS/EMIS Web as well as review of the appointment system to capture patient engagement as defined in section 4.1.3.

For HCV or HBV patients that require immediate therapy, oral and injectable medication adherence will be monitored and logged as detailed by clinical assessment of the patient's condition. Overall assessment of adherence will completed at 12 month follow up by the research team.

4.6 Laboratory Assessments(see section 5 for further information)

4.7 End of Study Definition

The end of study will be defined when the final patient has been assessed for engagement, and is documented as attending or not attending their 12 month follow up.

4.8 Subject Withdrawal

Subjects have the right to withdraw consent at any time and those who do so will have no further contact with the study team. Where feasible, reason for withdrawal will be documented.

4.9 Data Collection and Follow up for Withdrawn Subjects

Patients that withdraw consent or drop out will be replaced and the withdrawal will be documented, e.g. CRF and the medical records.

5. Laboratories

5.1 Local Laboratories

Blood samples will be taken from local sites phlebotomy and sent to local virology laboratories for analysis.

Blood samples will be measured for HbsAg and Anti-HCV as part of the screening process.

GP practices and local virology laboratory teams will liaise closely to ensure that participants that screen receive their result, as per standard practice. GPs will make the virology team aware of patients that consent to the HepFree trial. As the screening outcome directly relates to the primary objective of this study, the HepFree research team will liaise with both the GP practices and virology laboratories to ensure that screening outcome is captured accurately for participants. The identity of the participants will not be disclosed to the HepFree research team as the screening results will be linked to an anonymised number.

6. Safety Reporting

6.1 Serious Adverse Event Reporting

In non-CTIMPs a serious adverse event (SAE) is defined as an untoward occurrence that:

a) Results in death
b) Is life threatening
c) Requires hospitalization or prolongation of existing hospitalization
d) Results in persistent of significant disability or incapacity
e) Consists of a congenital abnormality of birth defect
f) Is otherwise considered medically significant by the investigator

An SAE occurring to a research participant should be reported to the main REC (i.e. the REC that gave a favourable opinion of the study) where in the opinion of the Chief Investigator the event was:

a) Related – that is, it resulted from administration of any of the research procedures and
b) Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence

Any hospitalization or other SAE that in the opinion of the CI is ***related*** to the trial and ***expected*** for this population will not be reported to the sponsor or the REC.

SAEs however that are deemed to be related to the trial and/or unexpected will be reported to both the sponsor within 24 hours of the CI becoming aware of the event and the REC within 15 days of the CI becoming aware of the event.

6.2 Adverse event reporting

In non-CTIMPs, an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject exposed to a research procedure which does not necessarily have a causal relationship with that procedure.

An adverse event can therefore be any unfavourable and unintended sign or symptom of disease temporarily associated with their exposure to a research procedure whether or not related to that procedure.

7. Statistical Considerations

7.1 Sample Size

We have assumed an intra-cluster correlation co-efficient of 0.05 for all outcomes and a coefficient of variation of cluster size of 0.65. The sample size is driven by the second stage trial, primary comparison, since this involves a smaller number of practices and patients. We assume that 40% of patients will be screened and of these 3% will test positive. To detect a difference from 50% to 70% engaged; with 90% power at the 5% significance level requires 55 practices which also accounts for drop outs. With the number of practices in each of the standard care/community care arms, the control practices will be able to detect an increase in screening from 15% to 40% with 90% power (first stage of the trial) which will allow for drop outs.

7.2 Statistical Analysis

No interim analyses are planned. A 5% level of significance will be used. Due to the nature of the outcomes we anticipate few missing values. We will use available case analysis, ie all individuals on whom we have outcome data.

Baseline comparisons of both cluster and individual characteristics will be presented. We will report separate analyses using generalized estimating equations for the main analyses for our three comparisons as follows:-

7.3.1 Primary Endpoint Effectiveness Analyses

Stage 1:

A) Control vs intervention screening, outcome = testing rates

Generalised estimating equations using logit link to account for binary outcome as primary analysis, accounting for region, cluster size (number of individuals eligible to be tested) A cluster-level t-test as sensitivity analysis.

B) Standard invitation v enhanced invitation (outcome = testing rates

Generalised estimating equations using logit link to account for binary outcome, accounting for region, cluster size (number of individuals eligible to be tested).

Stage 2:

Main comparison: Standard treatment v treatment in community outcome = engagement rates. Generalised estimating equations using logit link to account for binary outcome as primary analysis, accounting for region and cluster size.

7.4 Secondary Endpoint Effectiveness Analysis

Stage 2 of the trial: Adherence will be analysed using the same principles as discussed in section 2.1.

We will use the intention to treat principle when identifying which clusters and arms to analyse individuals in. Thus if patients switch between practices before their test results are available they will be analysed in the practice they were in when randomization took place in relation to the first stage of the trial comparison and B but in the practice to which they moved to in relation to comparison C (because at this stage the trial to test the effect of community care on engagement will not have started).

8. Data Handling & Record Keeping

8.1 Data Management

For stage 1 of the trial electronic data capture will be supported by the in-house GP practice database, such as EMIS WEB and SystemOne, by a HepFree specific template. Only authorized personnel will have access to the EMIS/SystemOne database at the practice level. Data relating to the primary outcome will be collected in an identical way between control and intervention practices. In intervention practices data from participants who have agreed to share personal data with the trial team will be included in the cost effectiveness analysis.

Data files containing HepFree specific data will be transferred from the GP practices to the HepFree data management team via a method deemed secure and in accordance to information governance policy.

Once HepFree data files are securely received by the data manager they will be uploaded onto a dedicated folder on the secure virtualised environment at the Barts Cancer Centre (BCC). This is where all data analysis of PCTU trial data is carried out. The BCC environment requires a two factor authentication to access the portal via Citrix and the folders where the data is stored are only accessible to the appropriate members of the PCTU and HepFree trial team.

The data files will be imported into a template Access database, within the BCC network, where various data integration steps will be performed to remove any duplication, standardise and ensure data quality.

For Stage 2 of the trial, trial specific data will be collected using Case Report Forms within an electronic data capture program hosted by a secure online data management system called OpenClinica. The CRFs can be accessed via an encrypted and secure uniform resource locator (URL) using a unique username and password, which is externally validated, and the details of the validation will be held in electronic files by the PCTU. Only authorised members of the HepFree team, who are fully trained, will be granted user accounts. A full audit trail will be accessible to data managers at the PCTU and relevant members of the HepFree team. The

OpenClinica software is provided by OpenClinica and is hosted on a server by their hosting partner in the UK.

The trial statistician will receive a fully integrated dataset which is blinded to GP trial allocation and GP location (South or East London or Bradford).

For the Pre-screening survey paper questionnaires will be used in the first instance. Data from these questionnaires will be entered into an OpenClinica database in the same way as described for Stage 2 of the trial above. The electronic survey will be designed to mirror the paper survey to ensure data is transferred accurately.

The HepFree team will implement a data management plan, which will be approved and overseen by the PCTU, to ensure data security, quality and accuracy.

8.1.1 Confidentiality

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

All documentation containing patient identifiable data (PID), such as informed consent forms and contact details, will be stored separately from case report forms, adverse event logs.

8.2 Study Documents

- A signed protocol and any subsequent amendments
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)Indemnity documentation from sponsorConditions of Sponsorship from sponsor Conditional/Final R&D

Approval Ethics submissions/approvals/correspondence CVs of CI and site staff

- Laboratory accreditation letter, certification and normal ranges for all laboratories to be utilised in the study Delegation log Enrolment log
- Study specific and PCTU SOPs

8.3 Case Report Form

All parameters relating to testing and engagement will be captured on eCRFs

8.4 Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years. For trials involving BLT Trust patients, undertaken by Trust staff, or sponsored by BLT or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre which is based at 9 Prescot Street. Site files from other sites must be archived at that external site and cannot be stored at the Modern Records Centre.

8.5 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

8.6 Clinical Governance Issues

8.6.1 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the

Committee must be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

8.7 Quality Control and Quality Assurance

8.7.1 Summary Monitoring Plan

Will be in accordance with the sponsor based risk assessment and monitoring will follow sponsor and PCTUSOPs.

8.7.2 Audit and Inspection

Auditing: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

A study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.

2. An individual investigator or department may request an audit.

3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.

4. Projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects.

5. Projects may be randomly selected for audit by an external organisation.

Internal audits will be conducted by the sponsor as per their SOPs and by the PCTU Quality Assurance Management team.

8.8 Non-Compliance

A noted systematic lack of both the CI and the study staff adhering to sponsor and PCTU

SOPs and the protocol leads to prolonged collection of deviations, breaches or suspected fraud.)

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The PCTU will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the JRO will agree an appropriate action, including an on-site audit.

9. Trial Committees

9.1 Trial Steering Committee

There are plans to have a steering committee in place for the study. It is intended that the committee will meet at least twice a year to review progress. They will have the authority to halt the program for reasons of non-progression or unacceptable ethical/safety issues.

9.2 Trial Management Committee

There will also be a management group put in place for this study which will meet three times annually. The management group will monitor progress and will implement any modifications the conduct of the study as appropriate, to be submitted to ethics for their approval.

9.3 Trial Team Meetings

HepFree team meetings will be scheduled on a weekly basis to review study progress and address any issues that may arise. If necessary the trial team will report the Trial Management Committee and the Trial Steering Committee.

10. Publication Policy

All publications from the study will be published with joint authorship. No member of the study team may publish any data from the study without the express consent of the management committee.

11. References

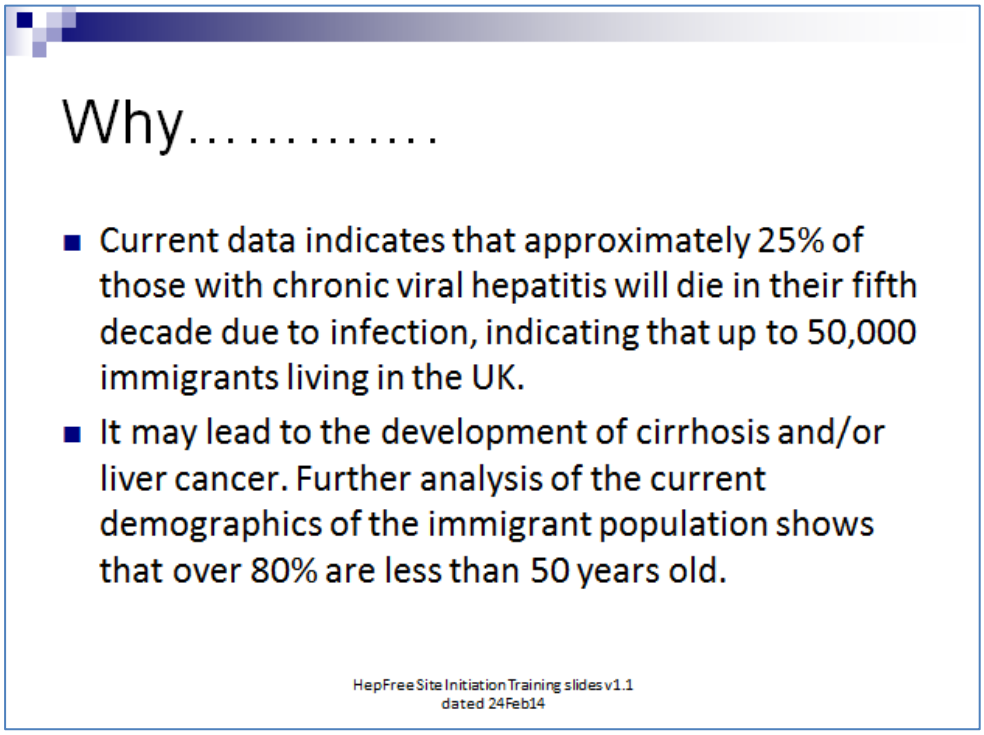
- Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. Stephen Ryder Gut 2004;53:451-455
- Cluster randomised trials: Methodological and ethical considerations MRC *clinical trials series* November 2002
- Uddin et al (2010) Prevalence of chronic viral hepatitis in people of south Asian ethnicity living in England: the prevalence cannot necessarily be predicted from theprevalence in the country of origin. J Viral Hepat;17(5):327-35
- Brabin et al (2001) Hepatitis B prevalence among Somali households in Liverpool

Appendix 1– Information with regards to Safety Reporting in Non-CTIMP Research

	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of learning of the event -Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor and MREC Immediately Within 3 days	By phone Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be	Main REC with a copy to be sent to the sponsor

			included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	

Appendix 2: The presentation handout distributed to all staff at the site initiation visit



The Aim

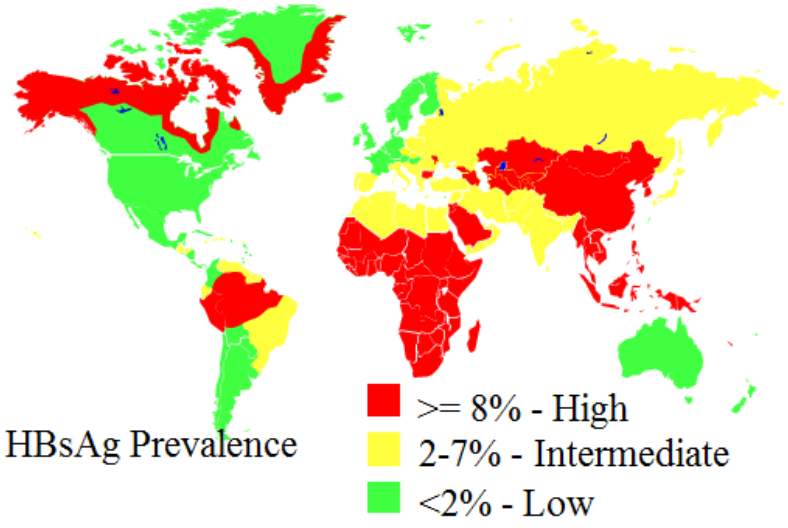
- We are hoping to recruit 72 GP practices within areas with an established immigrant (first/second generation (WHO classification of HBV prevalence >2%) population, namely in East and South London as well as Bradford.

Who is Eligible?

- **Inclusion Criteria:-**
- - Female and male patients who have been identified as first generations immigrants born in a country of high risk or second generation immigrants. (as outlined by WHO classification of HBV prevalence >2%)
- - >18 years of age

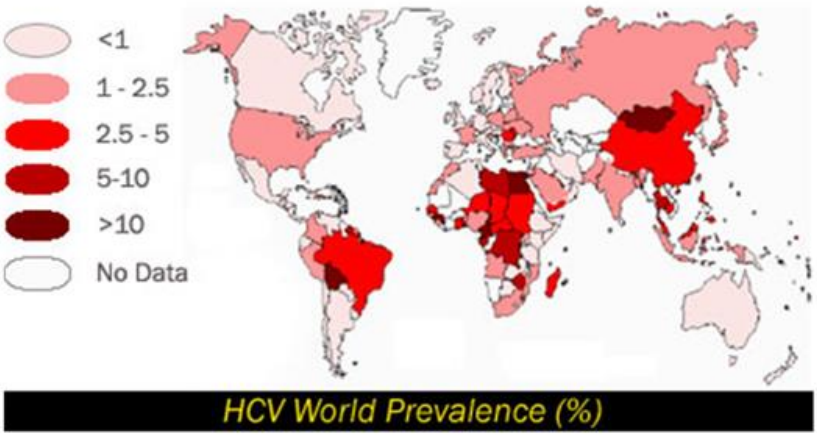
- **Exclusion Criteria**
- -<18 years old
- - Lacking capacity

HBV Prevalence



HepFree Site Initiation Training slides v1.1
dated 24Feb14

HCV Prevalence



HepFree Site Initiation Training slides v1.0
dated 25Sept13

HepFree Objectives

Primary Objectives

- To determine whether interventional screening is more effective than 'ad hoc' screening in the detection of ethnic minority patients with viral hepatitis.
- To determine whether the provision of an enhanced patient information invitation letters increases attendance for testing when compared to standard information invitation letter.
- To determine whether community based therapy is superior to conventional delivery of treatment (based on referral to local treatment centres) as measured by engagement with management

Secondary Objectives

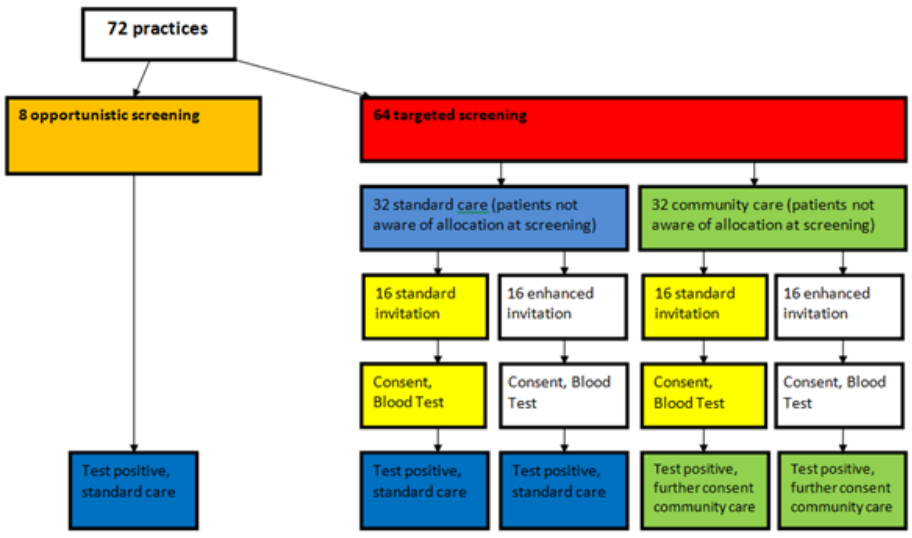
-To assess treatment compliance between patient groups receiving treatment within the community care setting against standard hospital care.

-To determine the cost effectiveness of the interventions

-To determine the prevalence of viral hepatitis in different ethnic groups living in the UK

HepFree Site Initiation Training slides v1.1
dated 24Feb14

The set up……



HepFree Site Initiation Training slides v1.1
dated 24Feb14

Standard vs Enhanced Invitation

-The enhanced invitation geared towards this potential participant demographic.

-Included patient public involvement (PPI) with focus group work with the help of local groups from the Chinese, African, Pakistani, Roma Communities looking into the stigmas/current understanding and perceptions surrounding viral hepatitis (B&C)

-The detailed tailored information on this invitation is postulated to have an impact on screening testing uptake.

Hospital vs Community Care

- Once screened and if testing positive, depending on GP randomisation allocation, patients will be referred as per standard care route to the local hepatology specialist care unit.
- Alternatively, patients will be referred to 'Interventional' community based practices will be set up within the communities. These patients will fall under the main care of the local hepatology specialist nurse, in consultation with the local hepatology consultant and their GP as to their monitoring/treatment.

What does this mean for GPs?

-Control practices?

-Hepatitis training from local specialist hepatologist.

-Practices asked to screen potential patients as per local practice.

-Once screening period complete, aggregated data about testing and follow up will be collected.

What does this mean for GPs?

-Targeted practices?

-Using GP database to identify potential participants, generate list and email out invitations.

-Obtained written informed consent from those who express interest in screening (all relevant staff to review HepFree informed consent document).

-Informing patient of result. If positive, patient attends GP and referred to either local specialist hepatology unit at hospital or 'interventional' GP practice where they will further assessed for disease status, undergo regular monitoring and/or commence anti-viral treatment over the course of 12 months.

Importance of not introducing selection bias

- All patients that are eligible for the study should be invited to take part, not just those who are 'more likely' to give consent and engage in treatment.
- Important to give consistent information using the PIS/informed consent checklist.
- It is extremely important that potential patients are not aware of the standard hospital care/community care allocation at the beginning as it may impact on the patient's decision to be screened.
- Patients are made aware of allocation only when required. i.e. ***If/ When Patient tests positive for either HepB/C.*** Additional written consent for community based care will be requested at this time.

Data Protection

- Data Protection Act 1998 is to use the minimum personal data to satisfy a purpose and to strip out information relating to a data subject that is not necessary for the particular processing being undertaken.
- **Personal Identifiable Data (PID)** – is any information that can identify a person. This could be one piece of data for example a person's name or a collection of information for example name, address and date of birth.
- **Primary Use - when information is used for healthcare and medical** purposes. This would directly contribute to the treatment, diagnosis or the care of the individual including relevant supporting administrative processes.

- Secondary Uses - research purposes, audits, etc,
- When PID is used for secondary use such as research this should be limited and de-identified ie Pseudonymised or anonymised
- Pseudonymisation – The technical process of replacing person identifiers in a dataset with other values (pseudonyms) from which the identities of individuals

- This allows the collection and access of research study data for analysis with data access pertinent to their research role as reflected in Caldicott Principles;

Access should be on a need to know basis.

-Therefore, if there is any correspondance with a third party (ie anyone outside direct clinical care team) – Use specific patient study identifier code (ie the EMIS Web and remove any patient identifiable data ie DoB, address, NHS number.

Research Governance

- Department of Health's *Research Governance framework* set out guiding principles and standards for conducting research in a healthcare or social/community setting first brought out in 2001.
- Increases ethical and scientific quality.
- It promotes good practice and ensures high quality research.
- It aims to reduce adverse events.
- It also prevents poor performance and mis conduct.
- It helps improves public confidence in research.

Research Governance standards

- Ethics – Consent – Participant understands the nature of the research, involvement, benefits as well as risks.
- Science – high quality research.
- Information – Data Protection
- Finance – Declaration of any financial interests
- Health and Safety – Patient Safety

Good Clinical Practice – Good Research Standards and how they can be applied

- **Informed Consent**

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form".

- To be formally documented in patient notes, with copy to kept in file/with notes

Study Documentation

- **Investigator File**, with all essential documents which "individually and collectively permit evaluation of the conduct of a study and the quality of the data produced"
- Should be kept with a safe secure locked location, with study specific access for the team. All members of the team should be aware of its location

Study Documentation

•**Training Log** – Staff documenting that they have been informed about the aims, objectives and the conduct of the study.
•**Site Delegation Log** – This ensures that the Lead GP (Principal Investigator) has oversight and delegates certain roles and responsibilities to members of his team that are trained and qualified to perform those tasks.
•**Protocol** – details the research design, methodology, aims, objectives, participant eligibility, data collection, data analysis.
•**Participant Information sheet** – This details the aims, benefits, risks and what is involved in participation within the study.
•**Participant Informed Consent** – This is agreement of understanding and participation within the study.
•**CVs** – to show that members of the study team are adequately qualified and trained for the roles and responsibilities that they have been delegated.

HepFree Site Initiation Training slides v1.1
dated 24Feb14

Pharmacoviligance - Adverse Events

- An **adverse event** (**AE**) is any untoward medical occurrence in a patient which does not necessarily have a causal relationship with this treatment.
- Serious Adverse Event serious adverse event (SAE) is defined as an untoward occurrence that:
- **(a)** results in death,
  (b) is life-threatening,
- **(c)** requires hospitalisation or prolongation of existing hospitalisation,
- **(d)** results in persistent or significant disability or incapacity,
- **(e)** consists of a congenital anomaly or birth defect, or
- **(f)** is otherwise considered medically significant by the investigator.

HepFree Site Initiation Training slides v1.0
dated 25Sept13

Pharmacoviligance Reporting

- An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:
- **Related** – that is, it resulted from administration of any of the research procedures, and
- **Unexpected** – that is, the type of event is not listed in the protocol as an expected occurrence

Pharmacoviligance Reporting

- Report immediately to Hepfree Study team.
- Chief Investigator to review and Study team to report to sponsor, if applicable.
- If deemed a SAE, REC to be informed within 15 days.
- Study team to complete form. May require further information from site.

Data Management Systems

- EMIS Web template to uploaded and activated within the practice, if targeted screening practice.
- Training to be given by member of the study team.
- If control practice – aggregated information will be collected at the study start and at the end. EMIS web searches to be provided.

Appendix 3: The HepFree trial invitation letters (standard and enhanced) version 1.0

[GP surgery address/ headed notepaper]

Dear Sir or Madam,

We are writing to you, from your local GP surgery, to ask if you would take part in a research project that we are undertaking.

We know that people who were born outside the UK and their children have a higher rate of infection with Hepatitis B and C Virus. Unfortunately, they are often "silent" diseases, and people are unaware that they are infected. These viruses can cause more serious liver illness that needs treatment. At the moment, we do not know the best way to identify the people who have Hepatitis B and C from amongst those who are at risk. This practice has therefore agreed to take part in a research project that will try to answer this question.

We are offering you a blood test for Hepatitis B and C. This will involve a short visit to your GP where a member of our team will discuss Hepatitis B and C. You can then decide what you would like to do. The blood taking itself takes only a few minutes. You will be informed about the results of all your tests. Should you be infected you will receive advice and will be assessed at your local specialist clinic and offered treatment, if necessary.

If you would like to talk about the project further or ask questions please contact the GP surgery. A member of the team may contact you to see if you would like to book an appointment to take part in the project, or you can call or attend your GP surgery. You can leave this project whenever you want without giving a reason and this will not affect your medical care.

Yours sincerely,

_____ _____

GP Hep Free/ QMUL rep

Appendix 3: The HepFree trial invitation letters (standard and enhanced) version 1.0

[GP surgery address/ headed notepaper]

Dear [Name of patient],

We are writing to tell you that your GP surgery is working on a new project with a research team from Queen Mary University of London.**The aim of the project is to encourage more people in London and Bradford to get a free test for Hepatitis B and Hepatitis C**. These are viruses that can affect the liver and may need treatment. It is very important that the Hepatitis B and C viruses are found and treated early, so that people can live a longer and healthier life. Your GP surgery and the research team hope to test people for Hepatitis B and C, so that we can offer advice and free treatment to people who test positive for Hepatitis B/C.

We would like to offer you the opportunity to have a free, simple blood test for Hepatitis B and C organised by your GP surgery. Receiving this letter does **not** mean that the GP thinks you are ill. Many other people from the GP surgery have also received this letter and have been offered the test.**We hope as many people as possible will take this opportunity for an important free health check.**

If you agree to have a Hepatitis B/C test, this will **involve a 10 minute visit to your GP surgery**. The GP will discuss hepatitis with you and organise the test. The test will draw a small amount of blood from your arm and this blood will only be tested for Hepatitis B/C.

Included on the back of this letter is an information sheet to tell you more about Hepatitis B and C. **If you would like to talk about the project further or ask questions please contact the GP surgery**. A member of the team may contact you to see if you would like to book an appointment to take part in the project, or you can call or attend your GP surgery. You can leave this project whenever you want without giving a reason and this will not affect your medical care.

Yours sincerely,

_____ _____

GP HepFree/QMULrep

What is Hepatitis B and C?

Many people in the world are infected with Hepatitis B and/or Hepatitis C. These are viruses that can infect the liver. When some people are infected with Hepatitis B or Hepatitis C they recover from the virus, but **for many people the virus will stay in their body for years.** This is then called chronic viral hepatitis.

How does someone get Hepatitis B/ Hepatitis C?

If a mother has the Hepatitis B virus, her child may be infected with the virus during or after birth. Hepatitis B can also be passed from one person to another through sexual contact.

Both Hepatitis B and Hepatitis C can also be passed from person to person by blood- through sharing razorblades, toothbrushes and non-sterilised needles. People may get Hepatitis B or C from medical treatment in a country where equipment is not properly sterilised.

What damage does Hepatitis B and C cause?

If the Hepatitis B or C virus remains in the person's body it slowly causes damage to their liver and the liver is damaged over many years. **If it is not treated, eventually it can cause liver cirrhosis (scarring of the liver and poor liver function), liver cancer and liver failure.**

What are the symptoms of Hepatitis B and C?

Some people with Hepatitis B or C might experience symptoms like tiredness, but **many people who are infected with the viruses do not have symptoms, and will not know that they are infected.** **The only way to know for sure whether you have Hepatitis B or C is to have a blood test for hepatitis.**

Why have I been invited for a test?

Receiving this letter does not mean that the GP thinks you are ill. We have sent this letter to many other people from the GP surgery in order to encourage as many people as possible to have a test for Hepatitis B and C.

Many people around the world are infected with Hepatitis B and Hepatitis C. **There are high rates of these viruses in countries in Asia, Africa and Eastern Europe, so people who move from these regions to the UK may be at increased risk of having these viruses.** It is very important that these viruses are found and treated, to promote healthy living and save lives.

What will happen if I go for a test?

If you agree to have a test for Hepatitis B and C, this will involve **a 10 minute visit to your GP surgery.** The GP will discuss hepatitis with you and take a small amount of blood to test for Hepatitis B and C. The test will be free of charge.

What will happen after the test?

Within 3 weeks, you will be contacted by the GP surgery, in order to receive the results of your test. **If the test shows that you have Hepatitis B or C then you will be offered advice and free treatment.** Your GP will discuss with you whether you will need to take medication to treat or manage the infection. Any treatment provided will be free of charge.

Confidentiality

Like all appointments at the GP surgery, if you decide to come for a test for Hepatitis B and C, your appointment will be completely confidential. The results of your test will be completely confidential and none of your family members or anyone else will be told.

Appendix 4: The HepFree trial patient information sheet version 5.0

Chronic Viral Hepatitis in First and Second Generation Immigrants from 'At Risk' Countries: The HepFree study

Patient Information Sheet for Patient Screening

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. It will tell you what will happen if you take part and what the risks might be. One of our team will go through the information sheet with you and answer any questions you have**.**It is entirely your choice whether or not you take part. Talk to others about the study if you wish.

1.0 Nature and purpose of the study

From previous research, we know that people who were born or whose parents were born in certain countries are often infected with viruses that can cause liver disease. But many people will be unaware of their infection, as the viruses often remain silent. We would like to identify people who have these viruses, so we can offer them treatment to try to prevent more serious liver disease. We do not yet know the best way to identify within certain 'at risk' populations, who are infected with chronic hepatitis and who are not, and this study is designed to answer this question.

Chronic Viral hepatitis – what is it and what does it do?

Chronic viral hepatitis is commonly caused by two viruses – hepatitis B and hepatitis C. Both of these viruses travel in blood and can be passed on by contact with another person's blood. Both viruses can be passed on by unsterile medical equipment and they can be passed on by mothers to their children. Chronic viral hepatitis may be a mild illness that does not cause any problems but sometimes chronic viral hepatitis causes liver disease that may need treatment. We have drugs that we can use to treat viral hepatitis and these work for most infected patients. Unfortunately, chronic viral hepatitis usually causes a silent disease and people who are infected often don't realise that they are infected until serious liver damage has occurred.

2.0 Why have I been invited?

We know from previous work that patients within certain communities have a higher likelihood/ are more at risk of having chronic hepatitis.

3.0 Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

4.0 What will happen to me if I take part?

In your GP practice, all selected patients will be invited. You may be contacted by your GP surgery to book an appointment for testing. If you would like to participate, one of the doctors will talk to you about viral hepatitis. You will then be asked to allow yourself to be tested for viral hepatitis. This will involve a small needle prick in one of your veins to draw 4 teaspoons (5 to 10ml) of blood which will then be sent to a local laboratory for testing. After testing the sample will be kept for the duration of the study as well as additional 2 years (to allow clinical tests to be performed in line with normal clinical management). Your visit to the practice should not take more than 10 minutes all together.Your GP will be informed of the results, and patients will be re-contacted to receive their results. If you don't have viral hepatitis no further action is needed. We will test only for viral hepatitis.

If you do have viral hepatitis you will be asked to attend a clinic where one of the doctors will talk to you about further tests that are needed. You may need treatment to protect your liver and the doctor who sees you in the clinic will explain this. You will be treated just like every other patient with viral hepatitis.

This is going to be a long term project and we will be collecting data and information held and managed by the Health and Social Care Information Centre and other central UK NHS bodies. This information may be used to provide information about your health status. This will not require us to contact you directly. If you do not wish to have long term data about you collected you are free to decline to take part in this part of the study.

5.0 What are the possible disadvantages and risks of taking part?

The study involves 10 minutes of your time to learn about viral hepatitis and you will be asked to allow us to take a blood sample. This is an uncomfortable procedure. You will have to wait for the results of the test and this can cause anxiety.

6.0 What are the possible benefits of taking part?

The aim of this study will hopefully tell us how best to identify people from high risk communities, who are infected with viral hepatitis.

Patients who participate in the study will learn whether or not they have viral hepatitis and if they do have viral hepatitis then they will be able to get treatment which may be helpful.

If you test positive for viral hepatitis, in line with standard practice, your GP will recommend your children to get tested for viral hepatitis. As part of the study, we would like to collect information about testing rates in children and so ask for your permission for access to this data.

7.0 What happens when the research study stops?

Nothing, you will continue to receive your clinical standard of care for your viral hepatitis.

8.0 What if there is a problem?

We believe that this study is safe and do not expect you to suffer any harm because of your participation. However, Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on balance of probabilities, an injury was caused as a direct result of interventions or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would have not happen if you were not participating in the study. These arrangements do not affect your right to pursue a claim through legal action. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and you can obtain advice on this, or any other aspect of the study from :- **Patient Advice and Liaison Service (PALS) Telephone:** is available Monday to Friday, 9.30am-4.30pm **Telephone:** 020 3594 2040**, E-mail:** pals@bartshealth.nhs.uk.

9.0 Will my taking part be kept confidential?

Your participation in this study will be kept confidential and your name will not be made known to anyone other than people working on the study. All information which is collected about you during the course of the research will be kept strictly confidential.

Your patient details and details about your health will be transferred from your GP practice to the study team at Queen Mary University of London, in a secure and confidential manner. The

study team will comply with information governance policy. Data collected as part of this study will be kept in a secure database and will only be accessible to authorised members of the HepFree Team. Professor Graham Foster will be responsible for the data that is collected as part of this trial (data custodian).

If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the patient rights you have under this Act.

10.0 What will happen to any samples I give?

All patients will need to have blood taken (about 4 teaspoons) in order to be tested for viral hepatitis. The sample will be sent to a local laboratory where it will be tested to see if you have ever been exposed to viral hepatitis and the length of time that you have had it. After completion of the study, it will be kept for 2 years (to allow clinical tests to be performed in line with normal clinical management).

11.0 Who is organising, funding and reviewing the research?

This study is being sponsored by Queen Mary, University of London and the funder is Department of Health. This research study has been reviewed by an independent group of individuals known as a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by NRES Committee London - Fulham Research Ethics Committee.

12.0 Further information and contact details

You are encouraged to ask questions at any time in the study. If you have a problem or concerns about the study or your rights as a subject, please call Prof Foster at 020 7882 7242**.**

Appendix 5: The HepFree trial consent form version 5.0

Chronic Viral Hepatitis in First and Second Generation Immigrants from 'At Risk' Countries: The HepFree Study

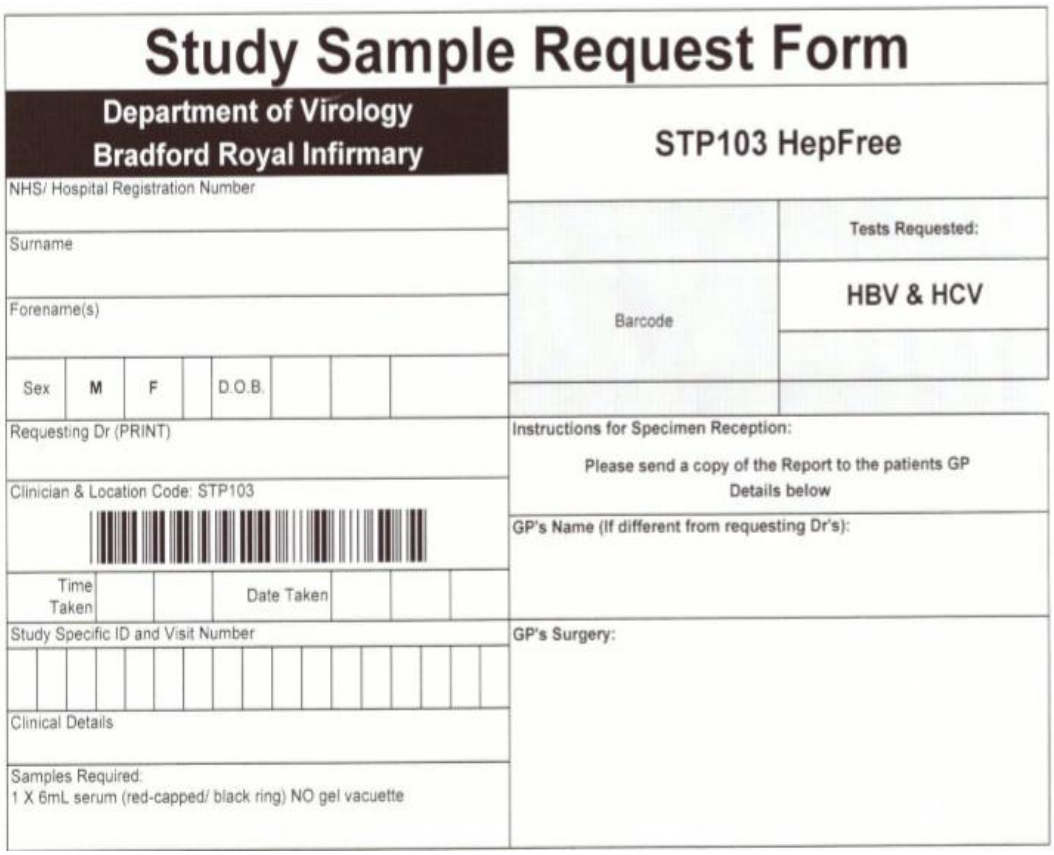
Consent Form Version 5.0 dated 27Mar2015

Centre (GP practice): Participant ID for this study:

Please initial box to indicate agreement	**INITIAL BELOW**
I confirm that I have read and understand the information sheet dated**27Mar2015**(version5.0) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from the Primary Care Trust/ Barts Health NHS Trust/Queen Mary, University of Londonor from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
I understand that data collected as part of the study has to be stored for 20 years and agree to this.	
I understand that if I test positive for viral hepatitis, it will recommended that all immediate family members get tested including children (if applicable). If this is applicable, I give permission for these individuals to have access to data to gather further information about testing rates in children.	
I understand and agree that information held and managed by The Health and Social CareInformation Centre and other central NHS bodies may be used in order to provide information about my health status.	
I agree to take part in the above study.	

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Investigator	Date	Signature

Appendix 6: The HepFree trial study specific sample request proforma version 2.0



Study Sample Request Form

Department of Virology
Bradford Royal Infirmary

STP103 HepFree

NHS/ Hospital Registration Number

Surname

Forename(s)

Sex | M | F | D.O.B.

Requesting Dr (PRINT)

Clinician & Location Code: STP103

Time Taken | Date Taken

Study Specific ID and Visit Number

Clinical Details

Samples Required:
1 X 6mL serum (red-capped/ black ring) NO gel vacuette

Barcode

Tests Requested:

HBV & HCV

Instructions for Specimen Reception:

Please send a copy of the Report to the patients GP
Details below

GP's Name (If different from requesting Dr's):

GP's Surgery:

Appendix 7: A list of countries with a prevalence of viral hepatitis of more than 2% (WHO)

Africa	
North Africa	**Southern Africa**
Algeria	Botswana
Egypt	Lesotho
Libyan Arab Jamahiriya	Namibia
Morocco	South Africa
Tunisia	Swaziland
East Africa	Zimbabwe
Burundi	**West Africa**
Comoros	Benin
Djibouti	Burkina Faso
Eritrea	Cape Verde
Ethiopia	Cote d'Ivoire
Kenya	Gambia
Madagascar	Ghana
Malawi	Guinea
Mauritius	Guinea-Bissau
Reunion	Liberia
Rwanda	Mali
Seychelles	Mauritania
Somalia	Niger
Uganda	Nigeria
United R. of Tanzania	Sao Tome and Principe
Central Africa	Senegal
Angola	Sierra Leone
Cameroon	Togo
Central African Republic	
Chad	
Congo	
D. R. of the Congo	
Equatorial Guinea	
Gabon	
Sudan	
Zambia	

Eastern Europe and the Newly Independent States of the former Soviet Union	
Albania	Lithuania
Armenia	Poland
Azerbaijan	Republic of Moldova
Belarus	Romania
Bosnia and Herzegovina	Russian Federation
Bulgaria	Slovakia
Croatia	Tajikistan
Czech Republic	T.F.Y.R. Macedonia
Estonia	Turkmenistan
Georgia	Ukraine
Kazakhstan	Uzbekistan
Kyrgyzstan	Yugoslavia
Latvia	
Western Europe	
Greece	Portugal
Italy	Spain
Malta	
The Americas	
Mexico and Central America	**Temperate South America**
Belize	Argentina
Guatemala	**Tropical South America**
Honduras	Bolivia
Panama	Brazil
The Caribbean	Ecuador
Antigua and Barbuda	Guana
Dominica	Suriname
Dominican Republic	Venezuela
Grenada	**Australia and the South Pacific Islands**
Haiti	American Samoa
Jamaica	C.N.Mariana Islands
Puerto Rico	Cook Islands
Saint Kitts and Nevis	Fiji
Saint Lucia	French Polynesia
St Vincent & Grenadines	Guam
Trinidad and Tobago	Kiribati
Turcs and Caicos Islands	Marshall Islands

East Asia	Micronesia
China	Nauru
D. People's R. of Korea	New Caledonia
Japan	Niue
Mongolia	Palau
Republic of Korea	Papua New Guinea
Middle East	Samoa
Bahrain	Solomon Islands
Iran (Islamic Republic of)	Tonga
Iraq	Tonga
Israel	Tuvalu
Jordan	Wallis and Futuna Islands
Kuwait	**Southeast Asia**
Lebanon	Brunei
Oman	Cambodia
Qatar	Indonesia
Saudi Arabia	Lao People's D. R.
Syrian Arab Republic	Malaysia
Turkey	Myanmar (Burma)
United Arab Emirates	Philippines
Yemen	Singapore
Indian Subcontinent and South Asia	Thailand
Afghanistan	Vietnam
Bangladesh	
Bhutan	
India	
Maldives	
Nepal	
Pakistan	

Appendix 8: The HepFree trial approval letters

NHS

West and South Yorkshire and Bassetlaw Commissioning Support Unit

Head of Research, Health Economics, Evidence and Evaluation Support
Paul Carder
Tel: 01274 237406
paul.carder@wsybcsu.nhs.uk

Senior Associate: Research
Rebecca Harper
Tel: 01274 237690
rebecca.harper@wsybcsu.nhs.uk

Professor Graham Foster
Professor of Hepatology
Centre for Digestive Diseases, Blizzard Institute
4 Newark Street
London
E1 2AT

Re: NHS Research Governance Assurance

Study Title: Chronic viral hepatitis in ethnic minorities. A controlled randomised cross sectional cluster trial to assess the impact of identifying, screening and treating immigrants with viral hepatitis (HepFree)

Ref no: 001_11_02_14_115023

Thank you for your recent submission to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit.

Following the successful completion of the Research Management & Governance (RM&G) process, we are pleased to provide assurance that all appropriate NHS research governance checks, including for the substantial amendment 1, minor amendment 1 and substantial amendment 3.0 for the study, have been completed for the following NHS Primary Care areas,:

Airedale, Wharfedale and Craven CCG
Bradford City CCG
Bradford District CCG

Please note – This letter assures independent contractors in the above areas that the Research Management & Governance (RM&G) process has been completed. Each independent contractor will decide whether to participate following this assurance and will confirm separately. Please also note that the first patients first visit for the study should happen no later than Thursday 13th March 2014.

The following conditions of assurance will apply:
You should be aware that assurance is granted subject to the conditions specified below:

- If required you must obtain an honorary contract and Letter of Access from NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit prior to commencing your study.
- Throughout the course of the study, all research activity should comply with relevant, current governance and regulatory requirements including (but not limited to)
    - The Research Governance Framework for Health and Social Care, 2nd Ed (2005)
    - The Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments
    - The Mental Capacity Act (2005)
    - The Ionising Radiation (Medical Exposure) (Amendment) Regulations (2006)
    - The Medical Devices Regulations (2002) (Statutory Instrument 2002/618)
    - The Human Tissue Act (2004)
    - The Data Protection Act (1998)

- Consent for NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit to monitor and audit your project, which is implicit in your acceptance of this assurance.
- Where any amendments, substantial or non substantial are made throughout the course of the study these should be notified to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit on the relevant form (available from http://myresearchproject.org)
- A copy of the final study report should be forwarded to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit on the relevant form (available from http://myresearchproject.org) no later than 3 months following study completion
- Should any serious adverse event(s) occur throughout the course of the study these should be notified to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit using the contact details set out above

Should you require any clarification regarding any of the points raised above, or have any further queries in relation to this assurance and post assurance study management process then please do not hesitate to contact Rebecca Harper on 01274 237690.

Finally, may we take this opportunity to wish you well with your study and look forward to hearing about your progress in due course.

Yours sincerely

E. Warren

Erica Warren
Principle Associate for Transformation: Experts and Research Service
NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit

The documents reviewed were:

Document	Version	Date
REC Favourable Opinion Letter	12/LO/1768	24 December 2012
Investigator CV – Professor Graham Foster		09 October 2012
Letter from Sponsor – Barts Health NHS Trust		11 October 2012
Letter of Invitation to Participant – Screening Invitation Letter	2.0	10 December 2012
Participant Consent Form: Tissue Storage	1.4	07 August 2007
Participant Consent Form: Patient Screening	2.0	05 December 2012
Participant Consent Form: Community Care	2.0	05 December 2012
Participant Information Sheet: Patient Screening	2.0	05 December 2012
Participant Information Sheet: Community Care	2.0	05 December 2012
Protocol	1.1	29 October 2012
REC Favourable Opinion Letter – SubAm1	12/LO/1768	28 March 2013
Declaration of Sponsorship Letter – Queen Mary University of London		30 January 2013
Evidence of Insurance/Indemnity – Arthur J Gallagher International	B1262FI0152813	29 July 2012
Participant Consent Form: Consent Form	2.1	22 February 2013
Participant Information Sheet: Participant Information Sheet for Patient Screening	2.1	22 February 2013
Notification of Substantial Amendment – SubAm1		14 March 2013
Covering Letter		15 March 2013
Protocol	2.1	22 February 2013
REC Acknowledgement Letter – MinorAm1	12/LO/1768	24 May 2013
Participant Information Sheet: Screening	2.2	23 May 2013
Notification of Minor Amendment – MinorAm1		23 May 2013
Protocol	2.2	23 May 2013
REC Favourable Opinion Letter – SubAm3.0	12/LO/1768	09 September 2013
Clarification re PHQ-9 Questionnaire		05 September 2013

Participant Consent Form	3.0	11 July 2013
Protocol	3.0	01 July 2013
Questionnaire: Health Literacy Questionnaire	Validated	
Participant Information Sheet	3.0	11 July 2013
Standard Screening Invitation Letter	3.0	11 July 2013
Questionnaire: PHQ-9	Validated	
Invitation for interview about knowledge about Hepatitis B&C	1.0	11 July 2013
Augmented Screening Invitation Letter	1.0	11 July 2013
Pre-screening Hepatitis B and C Survey	1.0	14 June 2013
Questionnaire: GAD-7	Validated	
Notification of Substantial Amendment – SubAm3.0		11 July 2013

Cc.
Dr. Sulleman Moreea
Consultant Gastroenterologist/Hepatologist
Bradford Royal Infirmary
Duckworth Lane
Bradford
BD9 6RJ

Bradford Teaching Hospitals NHS
NHS Foundation Trust

Version 4_ 19th July 2013

Enquiries on this matter should be made to:

The Research Management & Support Office
Bradford Institute for Health Research (BIHR)
Bradford Royal Infirmary
Duckworth Lane
BRADFORD
BD9 6RJ
Email: BradfordResearch.Applications@bthft.nhs.uk
Tel: 01274 36 (6808)/(4687)
Fax: 01274 38(2640)

Research Support & Governance Manager
Mrs Jane Dennison
Email: jane.dennison@bthft.nhs.uk
Tel: 01274 382575 (Direct)

Director of Research/BIHR
Professor John Wright
Email: john.wright@bthft.nhs.uk
Tel: 01274 364279 (Direct)

28th March 2014

Dr Sulleman Moreea
Consultant Gastroenterologist
Bradford Royal Infirmary

Dear Dr Moreea

NHS Permission Letter for Research at Bradford Teaching Hospitals NHS Foundation Trust

Re: Chronic viral hepatitis in ethnic minorities. A controlled randomised cross sectional cluster trial to assess the impact of identifying, screening and treating immigrants with viral hepatitis (HepFree)

Sponsor: Barts and The London NHS Trust
REC Ref No: 12/LO/1768
R&D Ref No: ReDA 1699
CSP Reference: 115023

Following submission of your Site-Specific Information form and supporting documentationseeking permission to conduct the above study at Bradford Teaching Hospitals NHS FoundationTrust (the “Foundation Trust”), I am pleased to inform you that your application has successfullycompleted an internal review process appropriate for this type of study and has satisfied ourresearch governance checks. A project record has been created on the Foundation Trust’sresearch database. You may commence research activities at the Foundation Trust in thelocations specified in your Site-Specific Information (SSI) form subject to the terms of this letter.The effective date of NHS permission for research is the date of this letter and this is the earliestcommencement date for research activities at the Foundation Trust. This letter supersedes allprevious letters you have received from us with regard to permission to proceed with thisresearch at Bradford Teaching Hospitals NHS Foundation Trust.

NHS permission for the above research has been granted on the basis described in theapplication forms, protocol and supporting documentation. The documents reviewed were:

Reviewed Documents –

Document	*Version*	*Date of document*
SSI form	115023/573572/6/256/204850/293629	
NHS R&D form	115023/441069/14/189	
Protocol	Version 3.0, dated 01 July 2013	
Patient Information Sheet: Screening	Version 3.0, dated 11 July 2013	
Participant Consent Form: Screening	Version 3.0, dated 11 July 2013	
Patient Information Sheet: Community Care	Version 2.0, dated 05 December 2012	
Participant Consent Form: Community Care	Version 2.0, dated 05 December 2012	
Participant Consent Form: TissueStorage	Version 1.4, dated 07 August 2007	
Ethics Favourable Opinion Letter		*24 December 2012*
REC Letter	Substantial Amendment 1 dated14/03/2013	28 March 2013
REC Letter	Minor Amendment 1 dated23/05/2013	24 May 2013
REC Letter	Amendment 3.0 dated 11/07/2013	09 September 2013

The site for which NHS permission for research is given is -

Bradford Teaching Hospitals NHS Foundation Trust

The terms referred to are:

1. You are the Principal Investigator or Local Collaborator for this Study and you are responsiblefor the conduct of this Study at this site.

2. NHS Indemnity applies to this Study with respect to negligent harm. However, NHS Indemnitydoes not provide compensation in the event of non-negligent harm.

3. This Study is a non-CTIMP (ie, **not** a clinical trial that involves an investigational medicinalproduct) and you may commence recruitment on receipt of this letter if you are ready to start.

4. Ongoing permission is subject to you adhering to the Trust's standard conditions of NHSPermission for research (attached).

5. You comply with the R&D Office's Oversight Plan as detailed below.

The approach taken for each Study shall be proportionate to the risks associated with the Studyand the level of monitoring and support being undertaken by the Sponsor. The R&D Office'sOversight Plan for this study is as follows –

1 Study Tracking
Please provide the R&D Office with –

a. Completed initial project status enquiry report sent to you directly from the R&D Officefollowing the NHS Permission Letter.

b. Completed Principal Investigator (PI) Annual Progress Report available from the Downloads section of the Bradford Institute for Health Research website atwww.bradfordresearch.nhs.uk due every year for the life of the Study on the anniversaryof the date of this letter.

c. Completed PI end of study declaration report (as defined in the protocol) (together withfinal recruitment figures for the Foundation Trust) available from the Downloads

section ofthe Bradford Institute for Health Research website at www.bradfordresearch.nhs.uk

d. Copy of amendment documentation and a copy of the REC and MHRA (if applicable)approval letters prior to implementing the changes at the Foundation Trust.

2 Issue Management –

a. Managing External Agreements.
b. Managing Internal Agreements.
c. Managing Study Processes.
d. Managing Research Passports

If an issue arises during the Study, please ensure you have a process in place to escalate thisand seek support from the R&D Office.

3 Audit -

The R&D Office performs a risk assessment prior to issuing this letter which provides theFoundation Trust with a risk-based approach to audit activities. The R&D Office undertakes toaudit at least 10% of its research projects each year. Priority will be given to studies with thehigher risk scores, clinical trials involving an investigational medicinal product(s) (CTIMPs),NIHR portfolio studies, and studies sponsored by the Foundation Trust. Some low risk studiesmay not be subject to scheduled audit at all. You will be informed by the R&D Office if ascheduled audit of this research study is planned in plenty of time (ie, at least six weeks' notice).

The R&D Office always has the option to conduct specific oversight activities at any time as theresult of any exceptional activity / events identified during the Study and failure to comply withthese terms may lead to suspension or termination of NHS Permission for research.

Please inform the R&D Office immediately should you have any concerns about patient safety orwellbeing with regard to research at the Foundation Trust.

If you have any queries during the conduct of your research, please do not hesitate to contactthe Research Governance Manager using the contact details provided at the top of this letter.May I take this opportunity to wish you well with your research Study.

Please help us to improve our service by completing the feedback form emailed previously to you and returning it to the R&D Office as soon as possible.

Yours sincerely

PROFESSOR JOHN WRIGHT

Director of Research/BIHR

Encs

cc CI/Sponsor/study co-ordinator

STANDARD CONDITIONS OF NHS PERMISSION FOR RESEARCH CONDUCTED AT BRADFORD TEACHING HOSPITALS NHS FOUNDATION TRUST (the "Foundation Trust")

1 Permission is granted to you, as the Principal Investigator/Local Collaborator, on theunderstanding that the study is conducted in accordance with the Research Governance Framework for Health & Social Care for England (the "Research Governance Framework") as varied from time to time and compliance by you with this Framework is a requirement of this NHS Permission for research. The Research Governance Framework describes roles and responsibilities of individuals and organisations involved in research including Investigator and Sponsor responsibilities. You can access the Research Governance Framework at – http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidanc e/DH_4108962 and the annex at - http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidanc e/Browsable/DH_088002.

2 In addition to complying with all the Foundation Trust's Policies and Procedures generally, in carrying out research you must comply with the Foundation Trust's local reporting requirements, systems, policies and procedures for implementing the Research Governance Framework (in particular, the Foundation Trust's Policy for Research). 3 The R&D Office will apply their escalation procedure to ensure action is taken for noncompliance of the Principal Investigator including where you do not take appropriate corrective and preventative actions for issues found in audits or requests for action by the R&D Office.

4 The Director may review the NHS Permission for research at any time in the light of any relevant information s/he receives.

5 Failure to comply with these conditions may lead to suspension or termination of NHS Permission for research and the relevant Research Ethics Committee shall be informed.

Your responsibilities shall include (applies to all types of research unless stated otherwise) –

Before the Study commences:

- **Research Approvals** The Principal Investigator is responsible for ensuring that the necessary approvals and trial registration (if applicable) are in place prior to commencing recruitment at the Foundation Trust. You may only use study documentation at the Foundation Trust that is the latest approved version by the Research Ethics Committee.

- **Study Processes & Research Standard Operating Procedures (SOPs)** The Principal Investigator (PI) is responsible for ensuring that Study initiation activities are satisfactorily completed at site so that the PI can ensure that all required study processes for the Foundation Trust are ready by the start of the study. The Research Management & Support Office (the "R&D Office") can advise and support you in defining relevant research standard operating procedures ("SOPs"). Research SOPs, templates, forms and guidance are provided by the R&D Office and are available on the Trust's Intranet research page.

- **Sufficient Time & Resources** The Principal investigator is responsible for ensuring there is sufficient time to complete the study within the time period; there is sufficient staff who are adequately informed; and there are appropriate facilities and equipment available as required by the protocol.

- **Study Personnel** The Principal investigator is responsible for ensuring that there is an adequate number of qualified staff (by education, training and experience) for the foreseen duration of the Study to conduct the Study properly in accordance with the regulations, Good Clinical Practice (GCP), Study protocol and SOPs where applicable. You should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial at the Foundation Trust. All staff involved in clinical trials involving investigational medicinal product(s) (CTIMPs) should undertake regular Good Clinical Practice (GCP) training, ie, every two years or sooner if there are changes to the regulations and/or guidance. Training in protocol procedures and study processes should be documented.

- **Site File** The Principal investigator is responsible for establishing and maintaining a Site File for the Foundation Trust which contains the study's Essential Documents and is readily available at all reasonable times for inspection. The Essential Documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and show whether the study is or has been conducted in accordance with regulatory and good clinical practice requirements (ICH GCP Handbook Section 8). The Site File should be appropriately labelled and sectioned with a contents page in accordance with the Sponsor's instructions. The Principal Investigator is responsible for archiving the Site File for a minimum of five years in a safe and secure place in accordance with the sponsor's instructions.

- **Delegation of Duties** The Principal investigator is responsible for maintaining a list of appropriately qualified persons to whom you have delegated significant study-related duties (the "delegation log").

- **Contracts/sponsor-site agreements** The Principal investigator is responsible for ensuring that the study's Clinical Trial Agreement (CTA)/sponsor-site agreement provided by the sponsor during study set-up is forwarded to the Research Management & Support Office (the "R&D Office") as soon as possible for review (including subsequent amendments). Where one exists, you should abide by the terms of the CTA/sponsor-site agreement and inform the R&D Office as soon as possible should you foresee any conflicts arising which might force a deviation from the agreement.

(For clinical trials that involve an investigational Medicinal Product(s)) -

- **Clinical Trials involving Investigational Medicinal Products (CTIMPs)** are regulated by the Medicines and Healthcare Products Regulatory Agency (MHRA). The Medicines for Human Use (Clinical Trial) Regulations 2004 as amended (the "UK Clinical Trial Regulations") which implement European Directive 2001/20/EC and European Directive 2005/28/EC (often called "the GCP Directive") set out the responsibilities of investigators and sponsors. The UK Clinical Trial Regulations are available from the Bradford Institute for Health Research (BIHR) website at www.bradfordresearch.nhs.uk or at www.ct-toolkit.ac.uk. The Principal Investigator is required to demonstrate to the MHRA GCP Inspectorate their compliance with the UK Clinical Trial Regulations and adherence to the conditions and principles of good clinical practice as provided in the Regulations (Schedule 1). You should be thoroughly familiar with the appropriate use of the investigational medicinal product (IMP). The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor, or when appropriate, of a qualified dentist.

  a. Prior to Commencing Recruitment The investigator is responsible for agreeing a start date with the Foundation Trust's Pharmacy Department before commencing recruitment. This is to ensure that Pharmacy Department have all procedures in place before the commencement of the trial.

(For research that involves a medical device(s)) -

- **Medical Devices** are regulated by the Medicines and Healthcare Products Regulatory Agency (MHRA). The Principal Investigator is responsible for ensuring that A Notice of No Objection is in place before utilising any medical device(s) in a research study at the Foundation Trust without a CE Mark, or if it is intended to utilise the medical device after modification(s), or utilised following changes to the CE mark intended purpose. If a medical device(s) is on loan for the purposes of the research, you are responsible for ensuring that the Foundation Trust's loan documentation has been successfully completed in accordance with

the Foundation Trust's policy on managing medical devices and the required electrical and safety tests have been completed before using the medical device(s) at the Foundation Trust.

(For research that involves the use of human tissue) -

- **The Human Tissue Act 2004** The Human Tissue Authority (HTA) regulates the storage, removal, use and disposal of human bodies, organs and tissue for a number of Scheduled Purposes (research being one of them) set out in the Human Tissue Act 2004. The HTA licenses organisations that store human tissue for research. Tissue for research can only be used with the person's consent. The HTA's Codes of Practice provide practical guidance and lay down the standards expected of investigators. (For research that involves a person who lacks capacity) -

- **The Mental Capacity Act 2005 for England and Wales** The Act sets out clear guidelines for research involving people who lack capacity. The research must be approved by an appropriate body, who will also ensure that the research is safe and relates to the person's condition. They must also ensure that the research would not be as effective if they use people who have mental capacity. The Principal Investigator is responsible for ensuring compliance with the Foundation Trust's policy for assessing capacity when assessing the capacity of research participants. During Study conduct:

- **Principal Investigator Oversight** The Principal Investigator is responsible for all study related activities at the Foundation Trust and should be fully aware of what is going on. You should have understanding and knowledge of the rules and regulations that govern research in the NHS.

- **Study Conduct & Good Clinical Practice (GCP)** The Principal investigator is responsible for the conduct of this research study at the Foundation Trust in accordance with the conditions and principles of good clinical practice. You may only conduct research in accordance with the relevant protocol, current marketing authorisation for the Investigational Medicinal Product or, as the case may be, the Clinical Trial Authorisation and the terms and conditions of the approval of the relevant Research Ethics Committee. Researchers should not deviate from the protocol unless for urgent safety measures and you should notify the sponsor immediately if this occurs.

(For clinical trials that involve an investigational Medicinal Product(s)) -

It is illegal for a person to conduct a clinical trial or perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with

that sponsor) otherwise than in accordance with the conditions and principles of good clinical practice (Regulation 28 (1)).

a. Serious Breaches You should report any serious breaches of protocol or GCP to the sponsor immediately in accordance with the sponsor's instructions (usually provided in the protocol). For the purposes of the UK Clinical Trial Regulations, a "serious breach" is a breach which is likely to effect to a significant degree –

i. the safety or physical or mental integrity of the subjects of the trial; or

ii. the scientific value of the trial.

b. Urgent Safety Measures The sponsor and the investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. You should report urgent safety measures immediately to the sponsor in accordance with the sponsor's instructions.

- **Amendments** The Principal Investigator is responsible for ensuring that changes to the study (ie, "Amendments") are not implemented at the Foundation Trust without first checking that the necessary research approvals are in place. You should notify the Research Management & Support Office (the "R&D Office") of all Amendments and provide the R&D Office with the amendment documentation including copies of the Research Ethics Committee (REC) approval letter(s) and Medicines and Healthcare Products Regulatory Agency (MHRA) authorisation letters (if applicable).

- **Notification of Adverse Events** The Principal Investigator is responsible for ensuring that –

a. For a clinical trial involving the use of investigational medicinal product(s) (CTIMP), the Foundation Trust will not accept delegation of sponsor pharmacovigilence activities relating to Regulation 33 of the UK Clinical Trial Regulations. Regulation 33 says it is the sponsor's responsibility to notify the licensing authority (ie, the MHRA) and the relevant ethics committee of suspected unexpected serious adverse reactions (SUSARs) which occur during the course of a clinical trial.

b. You (the investigator) are responsible for compliance with Regulation 32 of the UK Clinical Trial Regulations and you should follow the sponsor's instructions for recording and reporting adverse events in a timely manner. You are responsible for assessing causality. The causality given by you (the investigator) should not be over-ruled by the sponsor. If there is a disagreement, both opinions should be given.

c. For non-CTIMPs (ie, research that is not a clinical trial involving an investigational medicinal product(s)), the sponsor's instructions are complied with for recording and reporting adverse events to the sponsor within the specified timeframes.

d. Incidents are also reported in accordance with the Foundation Trust's Incident Reporting Policy and Serious Untoward Incident Policy in a timely manner using the Foundation Trust's Incident Reporting Form stating clearly in the text box that the incident is "research-related".

- **Research Monitoring & Reporting** The Principal Investigator is responsible for monitoring the conduct of the research study at the Foundation Trust on a day-to-day basis. The Foundation Trust is required to oversee monitoring of research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements. You should ensure that requests for reports on the progress and outcomes of the work by the Research Management & Support Office (the "R&D Office) or from those with a legitimate interest (such as the regulatory body, the sponsor, the funder(s), the Research Ethics Committee) are produced on time and to an acceptable standard and that all data and documentation associated with the study are available for audit at the request of the appropriate authority including the Foundation Trust.
- **Finance** The Principal Investigator is responsible for ensuring compliance with the Foundation Trust's Standing Orders and Standing Financial Instructions with regard to the management of research income and expenditure.
- **Honorary Research Contracts (HRC) and Letters of Access** The Principal Investigator is responsible for ensuring that anyone engaged in this research study at the Foundation Trust who:

a. is not employed by the Foundation Trust; and

b. interacts with individuals in a way which has a direct bearing on their quality of care holds a valid honorary contract issued by the Foundation Trust that covers the required research activity. Thus, for example, anyone who is not an NHS employee and will be involved directly in the diagnosis, care or treatment of a Foundation Trust patient involved in research will require an honorary research contract. Anyone who is not an NHS employee and will not be involved directly in the diagnosis, care or treatment of a Foundation Trust patient will not require an honorary research contract but may require a Letter of Access from the Foundation Trust giving them permission to attend the Foundation Trust's premises for the required purposes.

If you have been advised that you should complete a Research Passport application (or a member of your local research team), then you are responsible for ensuring that this is done and submitted in accordance with the Foundation Trust's procedure and the published Research Passport guidance. The relevant individuals must not commence any research activities involving the Foundation Trust until the appropriate employment contractual agreements are in place for them. You are responsible for actively monitoring professional registration of honorary research contract holders who are working under your **supervision.**

- **Intellectual Property** The Principal Investigator is responsible for informing the Research Management & Support Office (the "R&D Office) as soon as any intellectual property arises in order that it is appropriately managed in accordance with Foundation Trust's policy on managing intellectual property.

- **Health & Safety** The Principal Investigator is responsible for ensuring that the safety of participants and of researchers and other staff is given priority at all times, and health and safety regulations are being strictly observed. You should undertake or review (and document) a risk assessment with regard to this study and ensure that all work undertaken on behalf of or on Foundation Trust premises is managed in accordance with the Foundation Trust's risk management policies and procedures, seeking expert advice where necessary.

- **Changes to the Project Status and to the Membership of the Research Team** You should notify the Research Management & Support Office (the "R&D Office") immediately if you are no longer able to continue as Principal Investigator/Local Collaborator and/or if there is a change to project status such as a temporary halt or early termination.

- **Protocol Violation** Any protocol violation resulting from error, fraud or misconduct should be notified to the Foundation Trust using the Foundation Trust's policies and procedures for reporting incidents, fraud and misconduct. Suspected fraud should be reported to the local Counter Fraud Specialists for the Foundation Trust.

- **Data Protection & NHS Patient Confidentiality** The Principal investigator is responsible for compliance with the Data Protection Act 1998 and NHS patient confidentiality rules. You should make a reasonable and appropriate effort to understand any project issues that may arise due to the Data Protection Act 1998 and other legal provisions and guidance on handling information, seeking expert advice where necessary. You should ensure that the agreed counter measures as described in the protocol or other supporting documentation are kept in place for the life of the study (and for any agreed period after completion of the study) in order that you do not breach any of the principles outlined in the Data Protection Act 1998.

a. Identifying Suitable Participants and Seeking Consent -

i. Identifying suitable participants and making the first approach must be undertaken by a member of the clinical team responsible for treating the patient.

ii. The patient (or their legal guardian) should give explicit consent for the patient's personal information to be used for another purpose other than patient care, ie., research. As regards who obtains consent, it must be a member of the clinical care team, because to divulge personal information to the researcher (in order for the researcher to obtain consent) would be to breach the NHS rules on patient confidentiality. If the patient declines, their personal information (for instance their name and contact details) must not be passed to the researcher.

b. Transfer of Data for Research Purposes -

i.Access, copying and subsequent use of the Clinical Records ("Data Processing") shall be in accordance with the Protocol for the Study approved by the relevant Research Ethics Committee and in accordance with any terms and conditions specified by that Committee.

ii.In the event the Foundation Trust has approved the proposal subject to terms and conditions, the Data Processing shall be carried out in accordance with those terms and conditions.

iii.No copy of the Clinical Records or any part of them shall be removed or transferred from the Foundation Trust without first being anonymised. iv.Data Processing shall only be in accordance with the consent of the patient (or, in the case of a child, consent lawfully given on behalf of the child) obtained in accordance with the Protocol of this Study

After the Study finishes:

- **Dissemination** The Research Governance Framework says that researchers should open their work to critical review through the accepted scientific and professional channels. Once established, findings should be made available in an understandable format to those participating in the research (including relatives of deceased patients who have consented to the use of organs or tissue in the research) and to all those who could benefit from the research, through publication and/or other appropriate means. The Principal Investigator is

responsible for ensuring that feedback to their research participants is provided in accordance with the sponsor's instructions.

- **Archiving** The Principal Investigator is responsible for ensuring that there are suitable archiving arrangements in place at the end of the study that ensures the study's Essential Documents are safe and secure and are accessible on request by the sponsor, the Foundation Trust or any other authority with a legitimate interest. The minimum length of time that the study's Essential Documents should be kept for is 5 years.

(For clinical trials that involve an investigational Medicinal Product(s)) -

- **End of Trial Notification** The Principal Investigator should not accept delegation of sponsor responsibilities relating to Regulation 27 (end of trial notifications).

Appendix 9: The HepFree trial randomisation proforma version 1.0

	Protocol: HepFree GP Practice Randomisation Proforma

Lead GP Name (please complete below)
GP Practice Address (please complete below)
GP RegistrationPractice Code
GP Practice Registration Date (Date of when Practice agreed to participate in the study)
__ _/_ _ _/ _ _ _ _ (DD/MMM/YYYY)
Region (please circle one listed below)
A) East London (Newham, Tower Hamlets and WalthamForest) B) South London(Lambeth and Southwark) C) Bradford
Number of eligible patients
Please enter exact number below (if possible) _____ Please also circle the appropriate number grouping **A) = <1600** **B) = 1600-3300** **C) = >3300**
Site Identification Number (as generated by the randomisation programme)
Please enter below _____

Appendix 10: The HepFree trial treatment location contract version 1.0

Cluster Allocation Bias Training for GP Site Staff

HepFree is a CLUSTER RANDOMISED TRIAL. This means that Practices are randomised to the study, rather than individual participants. These types of trial are common in public health research and effective in the analysis of interventions, ranging from changes to health services to attitudes/behaviours of those involved.

-In HepFree, we are looking at participant uptake of Hep B/C screening and subsequent care and treatment for those testing positive, either in the ***usual local hospital setting*** or ***within the community***. Each practice has been allocated to either usual hospital care or community care, and we are looking at patient engagement.

IMPORTANCE OF AVOIDING BIAS BY INVITING ALL PATIENTS

-When patients come to the surgery following their screening invitation letters or via another route, it is important not to introduce bias. Bias could be introduced if only some patients were invited to take part in the trial of treatment. **All eligible patients should be invited to take part,** not just those considered 'more likely' to give consent to take part and engage well with treatment

-It is Important to give consistent information to potential participants (using the PIS/HepFreeinformed consent checklist) as well as addressing any queries. The HepFree team are available to assist.

-Remember that selection bias can be accidently introduced by tailoring study related information given that will pre-dispose the patient to give written informed consent and take part in the study.

IMPORTANCE OF AVOIDING BIAS BY GIVING EVERYONE THE SAME INFORMATION

-It is critical for the integrity of the study that potential participants do not know whether they are in the STANDARD HOSPITAL REFERRAL or COMMUNITY BASED CARE arm, until they have agreed to participate in the screening. This is a similar process to that in drug trials when participants are asked to consent to a trial without knowing which drug theywill receive.

-If potential participants know whether they will get STANDARD HOSPITAL REFERRAL or COMMUNITY BASED CARE, this may affect their decision to be screened and we may end up with different sorts of patients in the two arms of the study, again introducing bias.
-Thus, it is imperative to make sure that the participant is only made aware of the allocation when is required i.e. IF/WHEN PATIENT TESTS POSITIVE FOR EITHER HEP B and HEP C. Note that patients have the right to withdraw at this stage and may chose to be treated in hospital rather than the surgery
-WHEN the patient is found to have viral hepatitis and receives their result, they are made aware of the allocation and additional written consent for community based care is given. (Patients have the right to decline to participate)

-It is important that the patient is made aware that their care will be the main priority, irrespective of where it is received and it is ultimately their decision.

I confirm that I have read and understood the above information and will make every effort, on behalf of the GP Practice and all staff involved in the study, to ensure that bias is not introduced at any stage of the study.

_____	_____	_____
Name	Signature	Date

Appendix 11: The HepFree trial research specific curriculum vitae

CURRICULUM VITAE

Name:	
Present appointment: *(Job title, department, and organisation.)*	
Address: *(Full work address.)*	
Telephone number:	**Email address:**
Qualifications:	
Professional registration: *(Name of body, registration number and date of registration.)*	
Previous and other appointments: *(Include previous appointments in the last 5 years and other current appointments.)*	
Research experience: *(Summary of research experience, including the extent of your involvement. Refer to any specific clinical or research experience relevant to the current application.)*	
Research training: *(Details of any relevant training in the design or conduct of research, for example in the Clinical Trials Regulations, Good Clinical Practice, consent or other training appropriate to non-clinical research. Give the date of the training.)*	
Relevant publications: *(Give references to all publications in the last two years plus other publications relevant to the current application.)*	
Signature:	**Date:**

Appendix 12: The HepFree second stage consent form version 2.0

Chronic Viral Hepatitis in First and Second Generation Immigrants from 'At Risk' countries: The HepFree Study

Consent Form Version 2.0 dated 05Dec12

Centre (GP practice): Participant ID for this study:

Please initial box to indicate agreement

I confirm that I have read and understand the community care information sheet dated 05 Dec 2012 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
I agree to continuing my part in the above study.	

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of Person taking consent (if different from investigator)	Date	Signature

Appendix 13: The HepFree second stage patient information sheet version 2.0

Chronic Viral Hepatitis in First and Second Generation Immigrants from 'At Risk' Countries: The HepFree study

Supplementary Patient Information Sheet for Community Care therapy

We would like to invite you to continue to take part in our research study. Before you decide we would like you to understand what research is being done and what it would involve for you. It will tell you what will happen if you take part. One of our team will go through the information sheet with you and answer any questions you have**.**It is entirely your choice whether or not you take part. Talk to others about the study if you wish.

1.0 Nature and purpose of the study

You have previously read the patient information sheet for the screening component of this study, in which the nature and the purpose of the study have been previously highlighted. If you are reading this supplementary patient information sheet, it is because you have tested positive for viral hepatitis and have remained on study.

2.0 Do I have to take part?

It is up to you to decide to remain on study. We will describe the next stage of the study in this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

3.0 What will happen to me if I take part?

In your GP practice, all patients that test positive for viral hepatitis are to be referred to a community care practice for treatment, where you will be under the care of your GP, a specialist hepatitis nurse and a hepatology consultant. At this community based clinic, you will receive the same treatment as if you were referred to your local hospital specialist unit, like every other patient with viral hepatitis. This will not affect your treatment or subsequent medical care.

4.0 What are the possible benefits/disadvantages of taking part?

Patients that have viral hepatitis then they will be able to get treatment which may be helpful. You can receive your hepatitis treatment within a community based practice, or you can withdraw and continue treatment at your local hospital, as per standard of care.

5.0 What happens when the research study stops?

Nothing, you will continue to receive your clinical standard of care for your viral hepatitis.

6.0 What if there is a problem?

Provisions are the same as the screening component, regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or

treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you and you can obtain advice on this, or any other aspect of the study from :-Patient Advice and Liaison Service (PALS) Telephone: 020 7943 1335, Minicom: 020 7943 1350 E-mail: pals@bartsandthelondon.nhs.uk

7.0 Will my taking part be kept confidential?

Your continued participation, as before, will be kept confidential and your name will not be made known to anyone other than people working on the study. If you consent to take part the study will abide by the Data Protection Act 1998, and the patient rights you have under this Act.

8.0 Further information and contact details

You are encouraged to ask questions at any time in the study. If you have a problem or concerns about the study or your rights as a subject, please call Prof Foster at 020 7882 7242.

Appendix 14: The HepFree sub-study protocol version 2.0

Full Title: HepFree observational sub-study: The impact of chronic hepatitis C on healthcare utilisation.

Short Title/Acronym HepFree sub-study

SponsorQueen Mary, University of London

Representative of the Sponsor:

Dr Sally Burtles

Director of Research Services and Business Development

Joint Research Management Office

Queen Mary Innovation Centre

5 Walden Street

London

E1 2EF

Phone: 020 7882 7260

Email: sponsorsrep@bartshealth.nhs.uk

REC Reference010878

Chief Investigator Professor Graham Foster

The Blizard Institute

4 Newark St,

London,

E1 2AT

Insert as applicable list of localities

Bradford Clinical Commissioning Group (CCG)

Douglas Mill

Bowling Old Lane

Bradford

West Yorkshire

BD5 7JR

Contents Page

GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance

QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 2.0, dated 01/02/2016)**,or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Professor Graham Foster

Chief Investigator Site: Queen Mary University London

Signature and Date:  **01/02/2016**

Principal Investigator Agreement*(if different from Chief investigator)*

The clinical study as detailed within this research protocol **(Version XXX, dated XX XXX XX)**,or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

SUMMARY/SYNOPSIS

Short Title	HepFree sub-study
Methodology	Retrospective case control
Research Sites	Bradford Teaching Hospitals NHS Foundation Trust Participants will be recruited from all General Practices within Bradford City Clinical Commissioning Group which are participating in the HepFree trial and have been randomised to perform targeted screening.
Objectives/Aims	The primary aim of the HepFree sub-study is to investigate whether individuals with chronic hepatitis C who have been identified and diagnosed through the HepFree trial have made greater use of healthcare resources prior to diagnosis compared to individuals with a negative screening test.
Number of Participants/Patients	The sub-study will include all individuals who have consented to participate in the HepFree trial in Bradford and have had a positive screening test for hepatitis C between March 2014 and February 2016. Each case will be matched to a control; an individual who has consented to participate in the HepFree trial and tested negative for hepatitis B and C and who has been matched to the case using the following criteria: • Age • Sex • Ethnicity • Country of birth • Duration of time residing in the United Kingdom. The controls will be selected at random using an electronic randomisation function.
Main Inclusion Criteria	**Inclusion Criteria** - Participants that provide written informed consent to participate in the HepFree trial and have subsequently tested positive or negative for viral

	hepatitis C.All participants in the sub-study will have given consent to participate in the main HepFree trial. For Reference: The eligibility/inclusion criteria for HepFree is any person registered at a general practice performing targeted screening who: • Is aged 18 or older • Originates from, or is born to a parent originating from a country with a prevalence of viral hepatitis B of more than 2%. • Is able to give consent • Does not have a pre-existing diagnosis of chronic hepatitis B or C. For this sub-study we will define 'cases' as individuals who have either evidence of previous chronic hepatitis C infection, or individuals who have evidence of on-going chronic infection with hepatitis C. Controls are participants who have screened negative for hepatitis C and hepatitis B.
Statistical Methodology and Analysis (if applicable)	Pair wise comparison of cases and controls
Proposed Start Date	Data collection will start in February 2016 and include all participants who have been recruited into the trial since the start of recruitment in Bradford in March 2014.
Proposed End Date	Data will be collected on participants who are recruited into the main HepFree trial up to February 2016
Study Duration	The HepFree sub-study will collect retrospective data on all participants with a positive hepatitis C screening test and controls (with a negative hepatitis B and C screening test) who have been selected at random and who have participated in the HepFree trial between March 2014 and February 2016.

INTRODUCTION

Background

Hepatitis C is a single stranded, positive sense RNA virus belonging to the hepacivirus genus of the Flaviridae family. It is a blood borne virus with several routes of transmission. Globally, the major risk of transmission is through injecting drug use and more than 90% of cases are attributable to this (Helland, Sacks & Gold, 2009). In developing countries, the transfusion of unscreened blood products and transmission of the virus from unsterile injection methods pose the largest risk of infection (Kane et al, 1999). Spontaneous clearance of HCV happens in only a minority of cases, with approximately 75% progressing to chronic infection (Micallef et al, 2006).

Worldwide there are estimated to be between 130-150 million people chronically infected with hepatitis C and each year between 350,000 and 500,000 people die from hepatitis C related liver disease (World Health Organisation, 2014).

In cases of chronic infection with HCV there is slow evolution of fibrosis over many years culminating finally in cirrhosis (scarring of the liver resulting in chronic liver disease). Previous research has suggested that although inflammation is the major factor responsible for the development of fibrosis, its presence has no direct effect on the well-being of the individual (Seeff, 2002). There have been multiple publications assessing the impact of chronic HCV infection on quality of life which dispute this statement. Individuals with chronic HCV frequently report symptoms of fatigue, muscle ache and depression. Research performed on cohorts of cirrhotic and non-cirrhotic patients to attempt to establish the relationship between HCV infection, symptoms and the subsequent impact on quality of life have identified that fatigue is the most commonly reported extra-hepatic manifestation of chronic HCV (Tong et al, 1995; Barkheuizen et al, 1999; Cacoub et al, 1999; Poynard et al, 2002). The presence of fatigue and musculoskeletal pain in individuals with chronic HCV was significant when compared to the presence of these symptoms in individuals with liver disease of other aetiologies. As well as fatigue and musculoskeletal pain, a third commonly reported symptom in cohorts of patients with chronic HCV is depression. In a study by Gallegos-Orozco et al assessing quality of life performed in patients attending a tertiary referral centre, depression resulting in a reduction in quality of life was reported in 59% of those interviewed (Gallegos-

Orozco et al, 2003). Foster et al examined the effect of chronic hepatitis C on quality of life experienced using the short form 36 (SF36) symptomatology questionnaire (Foster et al, 1998). The SF36 outcomes were compared with a cohort of patients infected with chronic hepatitis B and a second cohort of healthy controls (Foster et al, 1998). In the HCV infected cohorts, SF36 scores related to mental and physical health domains were significantly reduced compared to the cohort of patients with chronic HBV in whom areas pertaining to mental health and general health perception only were reduced (Foster et al, 1998). These findings were supported in studies conducted by Carithers, Davis and Ware et al (Davis et al, 1994; Carithers et al, 1996; Ware et al, 1999). As well as having evidence that chronic infection with HCV has an adverse impact on quality of life and how patients feel, Interferon therapy and sustained virological response ('cure') has been shown to result in marked

improvements in quality of life and functioning (Bonkovsky et al, 1999; McHutchinson et al, 2001; Bini&Mehandru, 2006; Hollander et al, 2006; Bonkovsky et al 2007, Quarantini et al, 2008). The major limitation of previous research in this field is that symptomatology has nearly always been assessed in individuals with pre-existing knowledge of their diagnosis. In order to reduce reporter bias we plan to carry out an observational study using data from individuals who have consented to be involved in the HepFree trial. We will use data collected by the HepFree study and supplement it with information contained within patients medical records stored in the general practice surgery to establish what reasons prompted a visit to the doctor and to see if individuals with hepatitis C (who were identified through the HepFree trial and who were unaware of their diagnosis at the time) sought medical attention more frequently than age and sex matched controls who originate from the same country, are the same ethnicity and have resided in the UK for the same length of time(uninfected individuals).

HEPFREE SUB-STUDY TRIAL OBJECTIVES

Primary objective

The primary aim of the HepFree sub-study is to investigate whether individuals with chronic hepatitis C (hepatitis C antibody positive, RNA positive) who have been identified and diagnosed through the HepFree trial have made greater use of healthcare resources in primary care, prior to diagnosis, compared toindividuals with a negative viral hepatitis screening test.

Definitions

Chronic hepatitis C is defined as persistent infection with the virus for more than six months and is diagnosed by the presence of both a positive antibody and hepatitis C viral load test which looks for genetic material of the virus (RNA).
If an individual is hepatitis C antibody positive but RNA negative, this indicates that they have previously had exposure to the virus but have not developed chronic infection indicating spontaneous viral eradication (viral clearance without antiviral medication).

The primary aim of the sub-study will be addressed by collecting data for the following groups of participants

1) 'Cases' – participants who have consented to the HepFree trial and have had a viral hepatitis screen indicating chronic infection with hepatitis C (hepatitis C antibody positive, RNA positive).
2) 'Controls' – participants who have consented to the HepFree trial and had a viral hepatitis screen which is negative for hepatitis C and B. These participants will be matched to 'cases' using the following variables: age, sex, ethnicity, country of birth and duration of residence in the UK.
3) 'Cases of previous infection'- participants who have consented to the HepFree trial and had a viral hepatitis screen indicating previous exposure to hepatitis C (a screening result of hepatitis C antibody positive RNA negative) but no evidence of on-going infection.

The primary objective will be addressed by collecting the following data which will be used in conjunction with data collected by the main HepFree trial:

- The number of attendances to GP practices for each participant from 01/01/2005, or the point at which they enter the UK if it is after 2005.

If analysis of the data supports the hypothesis that individuals with chronic hepatitis C make greater use of health resources in primary care compared to healthy individuals with no evidence of infection, further analysis will focus on the clinical outcomes of the episodes of care.

Secondary objective

To establish whether individuals with evidence of previous infection with hepatitis C (hepatitis C antibody positive RNAnegative) have a greater number of episodes of care in primary care

compared to individuals with no evidence of previous infection (controls who have tested negative for hepatitis B and C through the HepFree trial).

METHODOLOGY

Inclusion Criteria

'Cases' are selected if they fulfil all of the following criteria below:

- All Participants who are registered at a HepFree intervention GP surgery
- Have provided written informed consent to take part in the HepFreetrial and
- Have evidence of chronic hepatitis C on testing carried out between March 2014 and February 2016.

The inclusion criteria for 'controls' and method of selection are listed below:

- A 'control' is a participant who has provided written consent to participate in the HepFree trial, has tested negative for both hepatitis B and C and fulfils the criteria below:
- Is born within a six month period of the 'case'
- Is the same sex as the 'case'
- Originates from the same country as the 'case'
- Is the same ethnicity as the 'case'
- Has resided in the United Kingdom for the same time period (+/- six months) as the case.

The inclusion criteria for 'cases of previous infection'

- All Participants who are registered at a GP surgery that is performing targeted screening and who have provided written informed consent to take part in the HepFree trial and have evidence of previous exposure to hepatitis C (a screening result of hepatitis C antibody positive RNA negative) but no evidence of on-going infection carried out between March 2014 and February 2016.

For reference, the eligibility/inclusion criteria for HepFree are any person registered at a general practice performing targeted screening who:

- Is aged 18 or older
- Originates from, or is born to a parent originating from a country with a prevalence of viral hepatitis B of more than 2%.
- Is able to give consent
- Does not have a pre-existing diagnosis of chronic hepatitis B or C.

A list of pseudoanonymised participant identifiers will be created for all controls that fulfil the inclusion criteria. From this list a single control will be selected at random by a computer generated randomisation programme.

Exclusion criteria

Data will not be collected for participants in the following situations:

- Individuals who have withdrawn consent to participate in the HepFree trial
- Individuals with a positive hepatitis C screening test (cases) who are 'lost to follow up'; including those who have failed to attend for study follow up events including diagnostic assessment in secondary care
- Individuals with a hepatitis C screening test which has been reported by the laboratory as 'indeterminate'.
- Individuals who die following recruitment to the study.
- Individuals who have had a screening test performed as part of HepFree despite having previously received hepatitis C eradication therapy in the past. In these cases the antibody to hepatitis C will remain positive despite a sustained virological response (the virus being 'cured').

Number of subjects and subject selection

Trial data and supplementary primary care attendance data will be collected and analysed for all first and second generation immigrants who have had a positive hepatitis C screening test as part of the HepFree study. This group will comprise of individuals who have on-going evidence of chronic hepatitis C infection (hepatitis C antibody positive, RNA positive) and those who have evidence of previous infection with hepatitis C but without evidence of on-going infection due to spontaneous clearance of the virus (hepatitis C antibody positive, RNA negative). 'Cases' will be matched to 'controls' using a 1:1 ratio and the method by which we will select controls is detailed above.

Based on the patterns of recruitment to the trial so far, it is estimated that 7500 individuals will be recruited and screened for viral hepatitis in GP surgeries across Bradford between March 2014 and February 2016. We estimate that as many as 1.6% will have a positive hepatitis C screening test based on a study performed by Uddin et al (Uddin et al, 2009). Using this prevalence data the sub-study may include up to 120 cases with a positive screening test.

Study design

The HepFree sub-study is a retrospective observational, case-control study which will use data collected from the HepFree trial, supplemented with data which is stored in medical records in primary care (a participant's general practice surgery).

Populations

As part of the HepFree sub-study, 'cases' are defined as individuals with a positive hepatitis C screening test who have been screened as part of the HepFree trial. Under this definition there are two types of 'case':

- Individuals with evidence of on-going chronic viral hepatitis C (hepatitis C antibody positive, RNA positive)
- Individuals with evidence of previous infection with chronic hepatitis C who do not have evidence of on-going infection which suggests spontaneous viral clearance (hepatitis C antibody positive, RNA negative).

'Controls' are defined as individuals who have consented for a viral hepatitis screening test as part of the HepFree trial who:

- Have tested negative for hepatitis B and C
- Who are of the same age as the 'case' (+/- six months).
- Who are of the same sex as the case
- Who were born in the same country as the case
- Who are the same ethnicity as the case
- Who have resided in the United Kingdom for the same length of time as the case (+/- six months).

Hypotheses

The HepFree sub-study has been designed to test the following hypotheses:

- Individuals with undiagnosed RNA-positive chronic hepatitis C are greater users of healthcare resources compared to individuals who do not have hepatitis C or hepatitis B.
- Individuals with evidence of previous infection with hepatitis C do not use healthcare resources any more often than individuals who have never had hepatitis C or hepatitis B.

Outcomes

We aim to test these hypotheses by comparing the number of episodes of care sought by 'cases' and comparing this to 'controls'. We intend to include all visits to the surgery from 2005 to see any of the following healthcare professionals:

- General practitioner (clinician)Specialist nurse practitioner
- Practice nurse, community nurse, district nurse
- Healthcare assistant.

Data will be collected on each episode of care and the following information will be collected:

- Date of attendance
- Healthcare professional consulted
- Diagnosis/outcome of the episode of care
- READ code diagnosis if available.

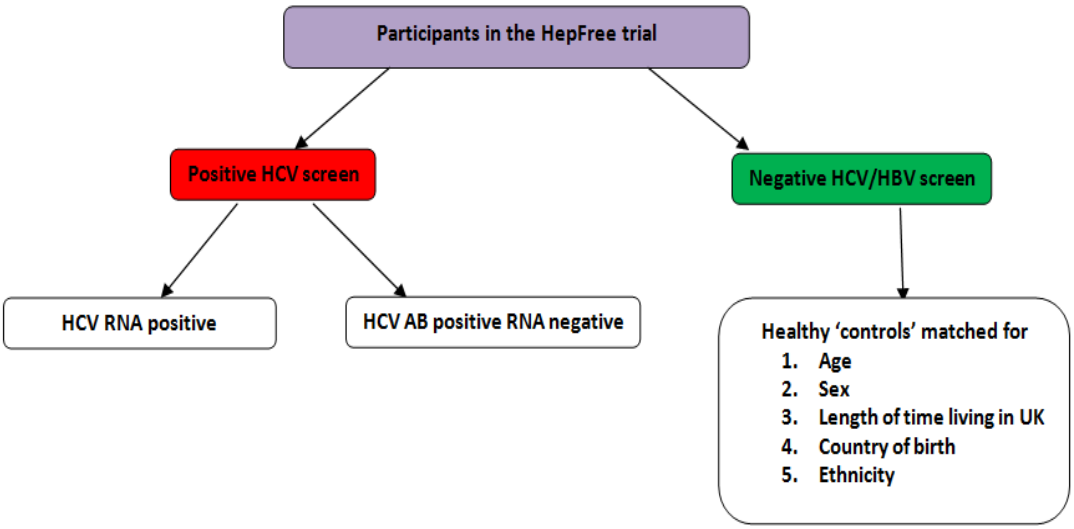
In addition to collecting information on the number of attendances we will collect information on the types of symptoms reported to establish which, if any symptoms are experienced more frequently in individuals with chronic hepatitis C.

Supplementary data from medical records on attendances to primary care is only available for the duration of time that the individual has been residing in the United Kingdom therefore this will vary from case to case. There is currently no data to suggest how long individuals will start to experience symptoms following hepatitis C infection. Supplementary information from medical records in primary care will be collected, where available, from 01/01/2005 to the point of HepFree screening test been performed. As comprehensive GP practice attendance began to be systematically recorded from 2005, the retrospective GP visit capture process will date back to 2005 where possible.

Study Design / Plan – Study Visits

Not applicable.
As described above.
Data collected as part of the HepFREE study will be used. This will be supplemented by accessing relevant medical records in GP practices to look retrospectively at attendances to the GP surgery. The sub-study does not require us to contact the study participants directly.

Study Scheme Diagram



STUDY PROCEDURES

Informed Consent

The consent form for the main HepFree trial (see appendix) includes signed approval for collection and use of data held and managed by the Health and Social Care information Centre and other central NHS bodies, including GP surgeries.

Schedule of assessment

Patients who have chronic hepatitis C will be monitored in secondary care using guidance from the HepFree study and local trust guidelines. Data collection for this study will not require additional patient contact.

End of study definition

The sub-study will include all participants with a positive hepatitis C screening test with either evidence of ongoing infection, or without evidence of ongoing infection and controls which

are matched according to the variables listed earlier in the protocol that have consented to participate in the HepFree trial between March 2014 and February 2016.

Subject withdrawal

Participants have the right to withdraw consent from the main HepFree trial at any time. Where possible the reason for revoking consent will be documented. Data collected from such patients will be discarded and will not be analysed.

Schedule of Assessment (in Diagrammatic Format)

See**Study Design / Plan – Study Visits**

STATISTICAL CONSIDERATIONS

Sample Size

The overall prevalence of a positive hepatitis C screening test in a similar study to HepFree performed by Uddin et al was 1.6%. This figure could indicate that the sample size of individuals with a positive hepatitis C screening test (including both RNA positive and antibody positive RNA negative) would be 120 based on 7500 participants screened). Cases would be matched 1:1 with controls indicating a final sample size of 240.

Method of analysis

We plan to analyse the data collected which has been described above in cohorts of patients with chronic hepatitis C and compare these findings with healthy controls. The same analysis will be performed for thecohort with evidence of previous infection but no evidence of on-going infection.

Paired samplesT-test will be used to test the following hypotheses:

- Individuals with undiagnosed RNA-positive chronic hepatitis C are greater users of healthcare resources compared to individuals who do not have hepatitis C or hepatitis B.
- Individuals with evidence of previous infection with hepatitis C who have now cleared the infection do not use healthcare resources any more frequently than individuals who have never had hepatitis C or hepatitis B.

ETHICS

Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee will be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

SAFETY CONSIDERATIONS

Not applicable – the application is purely for collection of data from pre-existing medical records for a research database.

DATA HANDLING AND RECORD KEEPING

Confidentiality

Data collected on primary care attendances will be stored in a password protected Microsoft database on a secure, NHS computer hard drive at Bradford Royal Infirmary (Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Lane, Bradford, DB9 6RJ). All data pertaining to participants will be stored under a unique study ID, separate from any patient identifiable data. The study ID is not identifiable outside of the participant's GP surgery. The study consent form is stored in the HepFreesite investigator file, in a locked room at the site of the consent (GP surgery). All data will bemanaged in accordance with the data protection

act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Any publications relating to this research database study will be anonymous.

Study Documents

- A sub-study protocol and any subsequent amendments
- A patient advisory group information sheet
- Current/Superseded Consent Forms from the main HepFree trial
- Indemnity documentation from legal entity
- Conditions of endorsement from R&D
- Conditional/Final R&D Approval Ethics submissions/approvals/correspondence
- CVs for CI and clinical fellow

Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years.

Compliance

The CI will ensure that the sub-study is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

LABORATORIES (if applicable)

Not applicable.

PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

Not applicable.

SAFETY REPORTING

Not applicable.

MONITORING AND AUDITING

Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee will be obtained and subsequently submitted to the JRO to obtain Final R&D approval.

Quality Control and Quality Assurance

Quality control of data is an integral part of all research and takes place during data collection, data entry and data checking.

Data collection

Data collected as part of the HepFree study is collected in accordance with the data management plan. The data collected is monitored and cleaned in accordance with PCTU and the Sponsor's requirements. Data which is collected from databases at GP surgeries in primary care is considered source data and will not be amended or modified in any way. The data which is collected from these databases in primary care by the clinical fellow who has authority and permission to access personal information of participants from the consent form. The clinical fellow has a letter of access granted to conduct research within the

Bradford City CCG NHS Primary Care area and permission has been granted by GP practices that signed up to the main HepFree trial. Data will be manually extracted and transferred into the research database. No data exports will be made.

Data entry

A standardised process will be used in cases of data been transcribed and entered into a Microsoft database to ensure quality control.

Trial committees

This study will be overseen by the HepFree trial committees – specifically the HepFree trial steering committee and the HepFree trial monitoring committee

Finance and funding

The funding body for the sub-study is the National Institute for Health Research and the budget code is: DDCH1A9R.

Indemnity

Not required.

Dissemination of research findings

All publications using data obtained as a result of the HepFree study will be published with joint authorship with express consent of the study management committee.

Anonymity of study participants will be maintained throughout.

REFERENCES

- Barkheuizen A, Rosen HR, Wolf S, Flora K, Benner K, Bennett RM. 1999. Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients. American Journal of Gastroenterology. Volume 94, issue 5, pages 1355-60.
- Bini EJ, Mehandru S. 2006. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. Alimentary Pharmacology & Therapeutics. Volume 23, issue 6, pages 777-85.

- Bonkovsky HL, Wooley JM, 1999. The Consensus Interferon Study Group. Reduction of health related quality of life in chronic hepatitis C and improvement with interferon therapy. Hepatology, vol 29, no. 1, p264-270
- Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, Kulig CC, Di Bisceglie AM, Morgan TR, Dienstag JL, Ghany MG, Gretch DR; HALT-C Trial Group. 2007. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. Journal of Hepatology. Volume 46, issue 3, pages 420-31.
- Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, Opolon P. 1999. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis &Rehumatology. Volume 42, issue 10, pages 2204-12.
- Carithers RL Jr, Sugano D, Bayliss M. 1996. Health assessment for chronic HCV infection: results of quality of life. Digestive Diseases and Sciences. Volume 31, issue 12 supplement, pages 75S-80S.
- Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, Carey W, Jacobson IM, Payne J, Dienstag JL. 1994. Assessing health-related quality of life in chronic hepatitis C using Sickness Impact Profile. Clinical Therapeutics. Volume 16, issue 2, pages 334-43.
- Foster GR, Goldin RD, Thomas HC, 1998. Chronic Hepatitis C Virus Infection Causes a Significant Reduction in Quality of Life in the Absence of Cirrhosis. Hepatology. Vol 27, no. 1, p 209-212
- Gallegos-Orozco JF, Fuentes AP, Gerardo Argueta J, Perez-Pruna C, Hinojosa-Becerril C, Sixtos-Alonso MS, Cruz-Castellanos S, Gutierrez-Reyes G, Olivera-Martinez MA, Gutierrez-Ruiz MC, Kershenobich D. 2003. Health-related quality of life and depression in patients with chronic hepatitis C. Archives of Medical Research. Volume 34, issue 2, pages 124-9.
- Hellard M, Sacks-Davis R, Gold J, 2009, Hepatitis C Treatment For Injection Drug Users: A Review of the Available Evidence. Clinical Infectious Diseases. Vol 49, no. 4, p 561-573
- Hollander A, Foster GR, Weiland O. 2006. Health-related quality of life before, during and after combination therapy with interferon and ribavirin in unselected Swedish patients with chronic hepatitis C. Scandinavian Journal of Gastroenterology. Volume 41, issue 5, pages 577-85.
- McHutchinson JG, Ware Jr JE, Bayliss MS, Pianko S, Albrecht JK, Cort S, Yang I, Neary MP the Hepatitis Interventional Therapy Group. 2001. The effects of interferon alpha-2b in vombination with ribavirin on health related quality of life and work productivity. Journal of Hepatology. Volume 34, issue 1, pages 140-147.
- Micallef JM, Kaldor JM, Dore GJ, 2006. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. Journal of viral hepatitis. Vol 13, no. 1, p 34-41
- Poynard T, Cacoub P, Ratzui V, Myers RP, Dezailles MH, Mercadier A, Ghillani P, Charlotte F, Piette JC, Moussalli J, for the multivirc group. 2002. Fatigue in patients with chronic hepatitis C. Journal of Viral Hepatitis. Volume 9, issue 4, pages 295-303.
- Quarantini LC, Miranda-Scippa A, Batista-Neves S, Galvao-de-Almeida A, Lacerda AL, Moriyama TS, Sampaio AS, Melcop AC, Schinoni MI, de Oliveira IR, Parana R, Bressan RA. 2008. The effect of early virological response in health-related quality of life in HCV-infected patients. Journal of Medical Virology. Volume 80, issue 3, pages 419-23.
- Seeff LB. 2002. Natural history of chronic hepatitis C. Hepatology. Volume 36, issue 5 supplement 1, pages 35-46.
- Tong MJ, el-Farra NS, Reikes AR, Co RL. 1995. Clinical outcomes after transfusion-associated hepatitis C. The New England Journal of Medicine. Volume 332, issue 22, pages 1463-6.

- Ware JE Jr, Bayliss MS, Mannocchia M, Davis GL. 1999. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. Hepatology. Volume 30, issue 2, pages 550-5.
- World Health Organisation, 2014, Hepatitis C Fact sheet No. 164 updated April 2014 [online] available from http://www.who.int/mediacentre/factsheets/fs164/en/

ICPC-2 – English

International Classification of Primary Care – 2nd Edition

WoncaInternational Classification Committee (WICC)

Process codes

-30 MedicalExam/Eval-Complete
-31 MedicalExamination/HealthEvaluation-Partial/Pre-opcheck
-32 SensitivityTest
-33 Microbiological/ImmunologicalTest
-34 BloodTest
-35 UrineTest
-36 FaecesTest
-37 Histological/ExfoliativeCytology
-38 OtherLaboratoryTestNEC
-39 PhysicalFunctionTest
-40 DiagnosticEndoscopy
-41 DiagnosticRadiology/Imaging
-42 ElectricalTracings
-43 OtherDiagnosticProcedures
-44 PreventiveImunisations/Medications
-45 Observe/Educate/Advice/Diet
-46 ConsultwithPrimaryCareProvider
-47 Consultation with Specialist
-48 Clarification/Discuss Patient's RFE
-49 OtherPreventiveProcedures
-50 Medicat-Script/Reqst/Renew/Inject
-51 Incise/Drain/Flush/Aspirate
-52 Excise/Remove/Biopsy/Destruction/Debride
-53 Instrument/Catheter/Intubate/Dilate
-54 Repair/Fixate-Suture/Cast/Prosthetic
-55 LocalInjection/Infiltration
-56 Dress/Press/Compress/Tamponade
-57 PhysicalMedicine/Rehabilitation
-58 TherapeuticCounselling/Listening
-59 Other Therapeutic Procedure NEC
-60 ResultsTests/Procedures
-61 ResultsExam/Test/Record
-62 AdministrativeProcedure
-63 Follow-upEncounterUnspecified
-64 Encounter Initiated by Provider
-65 Encounter Initiated third person
-66 Refer to Other Provider (EXCL. M.D.)
-67 Referral to Physician/Specialist/Clinic/Hospital
-69 OtherReasonforEncounterNEC

Generaland UnspecifiedA

A01 Paingeneral/multiplesites
A02 Chills
A03 Fever
A04 Weakness/tirednessgeneral
A05 Feelingill
A06 Fainting/syncope
A07 Coma
A08 Swelling
A09 Sweatingproblem
A10 Bleeding/haemorrhageNOS
A13 Concern/fearmedicaltreatment
A16 Irritableinfant
A18 Concernaboutappearance
A20 Euthanasiarequest/discussion
A21 Risk factor for malignancy
A23 Risk factor NOS
A25 Fearofdeath/dying
A26 FearofcancerNOS
A27 FearofotherdiseaseNOS
A28 Limitedfunction/disabilityNOS
A29 General symptom/complaint
A70 Tuberculosis
A71 Measles
A72 Chickenpox
A73 Malaria
A74 Rubella
A75 Infectiousmononucleosis
A76 Viralexanthemother
A77 Viral disease other/NOS
A78 Infectious disease other/NOS
A79 MalignancyNOS
A80 Trauma/injuryNOS
A81 Multipletrauma/injuries A82 Secondaryeffectoftrauma A84 Poisoning by medical agent
A85 Adverse effect medical agent
A86 Toxiceffectnon-medicinalsubstance
A87 Complicationofmedicaltreatment
A88 Adverseeffectphysicalfactor
A89 Effectprostheticdevice
A90 CongenitalanomalyOS/multiple
A91 AbnormalresultinvestigationNOS
A92 Allergy/allergic reaction NOS
A93 Prematurenewborn
A94 Perinatalmorbidityother
A95 Perinatalmortality
A96 Death
A97 Nodisease
A98 Healthmaintenance/prevention

Blood, Blood Forming Organs and Immune MechanismB

B02 Lymphgland(s)enlarged/painful
B04 Bloodsymptom/complaint
B25 Fear of aids/HIV
B26 Fearcancerblood/lymph
B27 Fearblood/lymphdiseaseother
B28 Limitedfunction/disability
B29 Sympt/complt lymph/immune other
B70 Lymphadenitisacute
B71 Lymphadenitisnon-specific
B72 Hodgkin'sdisease/lymphoma
B73 Leukaemia
B74 Malignantneoplasmbloodother
B75 Benign/unspecified neoplasm blood
B76 Rupturedspleentraumatic
B77 Injuryblood/lymph/spleenother
B78 Hereditary haemolytic anaemia
B79 Congen.anom. blood/lymph other
B80 Irondeficiencyanaemia
B81 Anaemia,VitaminB12/folatedef.
B82 Anaemiaother/unspecified
B84 Unexplained abnormal white cells
B87 Splenomegaly
B90 HIV-infection/aids
B99 Blood/lymph/spleendiseaseother

PROCESSCODES
SYMPTOMS/COMPLAINT
INFECTIONS
NEOPLASMS
INJURIES
CONGENITAL
OTHER DIAGNOSES

Digestive D

D01 Abdominalpain/crampsgeneral
D02 Abdominalpainepigastric
D03 Heartburn
D04 Rectal/analpain
D05 Perianalitching
D06 Abdominal pain localized other
D07 Dyspepsia/indigestion
D08
D10 Vomiting
D11 Diarrhoea
D12 Constipation
D13 Jaundice
D14 Haematemesis/vomitingblood
D15 Melaena
D16 Rectalbleeding
D17 Incontinence of bowel
D18 Changefaeces/bowelmovements
D19 Teeth/gumsymptom/complaint
D20 Mouth/tongue/lipsymptom/complt.
D21 Swallowingproblem
D23 Hepatomegaly
D24 AbdominalmassNOS
D25 Abdominaldistension
D26 Fearofcancerofdigestivesystem
D27 Fearofdigestivediseaseother
D28 Limited function/disability (d)
D29 Digestive symptom/complaint other
D70 Gastrointestinalinfection
D71 Mumps
D72 Viralhepatitis
D73 Gastroenteritispresumedinfection
D74 Malignantneoplasmstomach
D75 Malignantneoplasmcolon/rectum
D76 Malignantneoplasmpancreas
D77 Malig.neoplasmdigestother/NOS
D79 Foreignbodydigestivesystem
D80 Injury digestive system other
D81 Congen. anomaly digestive system
D82 Teeth/gumdisease
D83 Mouth/tongue/lipdisease
D84 Oesophagusdisease
D85 Duodenalulcer
D86 Peptic ulcer other
D87 Stomachfunctiondisorder
D88 Appendicitis
D89 Inguinalhernia
D90 Hiatushernia
D91 Abdominal hernia other
D92 Diverticulardisease
D93 Irritablebowelsyndrome
D94 Chronicenteritis/ulcerativecolitis
D95 Analfissure/perianalabscess
D96 Worms/otherparasites
D97 LiverdiseaseNOS
D98 Cholecystitis/cholelithiasis
D99 Diseasedigestivesystem,other

Eye F

F01 Eyepain
F02 Redeye
F03 Eyedischarge
F04 Visualfloaters/spots
F05 Visualdisturbanceother
F13 Eye sensation abnormal
F14 Eyemovementsabnormal
F15 Eyeappearanceabnormal
F16 Eyelidsymptom/complaint
F17 Glassessymptom/complaint
F18 Contact lens symptom/complaint
F27 Fearofeyedisease
F28 Limited function/disability (f)
F29 Eyesymptom/complaintother
F70 Conjunctivitisinfectious
F71 Conjunctivitisallergic
F72 Blepharitis/stye/chalazion
F73 Eye infection/inflammation other
F74 Neoplasmofeye/adnexa
F75 Contusion/haemorrhageeye
F76 Foreign body in eye
F79 Injuryeyeother
F80 Blockedlacrimalductofinfant
F81 Congenitalanomalyeyeother
F82 Detachedretina
F83 Retinopathy
F84 Maculardegeneration
F85 Cornealulcer
F86 Trachoma
F91 Refractiveerror
F92 Catara ct F93 Glauco
F99 Eye/adnexadisease,other

EarH

H01 Earpain/earache
H02 Hearingcomplaint
H03 Tinnitus,ringing/buzzingear
H04 Eardischarge
H05 Bleedingear
H13 Pluggedfeelingear
H15 Concernwithappearanceofears
H27 Fearofeardisease
H28 Limited function/disability ear
H29 Earsymptom/complaintother
H70 Otitisexterna
H71 Acuteotitismedia/myringitis
H72 Serousotitismedia
H73 Eustachiansalpingitis
H74 Chronicotitismedia
H75 Neoplasmofear
H76 Foreign body in ear H77 Perforationeardrum
H79 Ear injury other
H80 Congenitalanomalyofear
H81 Excessive ear wax
H82 Vertiginoussyndrome
H83 Otosclerosis
H84
H86 Deafness
H99 Ear/mastoiddisease,other

Cardiovascular K

K01 Heartpain
K02 Pressure/tightness of heart
K03 CardiovascularpainNOS
K04 Palpitations/awareness of heart
K05 Irregular heartbeat other
K06 Prominentveins
K07 Swollenankles/oedema
K22 Risk factor cardiovasculardisease
K24 Fearofheartdisease
K25 Fearofhypertension
K27 Fearcardiovasculardiseaseother
K28 Limited function/disability (k)
K29 Cardiovascularsympt./complt.other
K70 Infectionofcirculatorysystem
K71 Rheumatic fever/heart disease
K72 Neoplasmcardiovascular
K73 Congenitalanomalycardiovascular
K74 Ischaemic heartdisease w.angina
K75 Acutemyocardialinfarction
K76 Ischaemic heartdisease w/o angina
K77 Heartfailure
K78 Atrialfibrillation/flutter
K79 Paroxysmaltachycardia
K80 CardiacarrhythmiaNOS
K82 Pulmonary heart disease K83 Heart valve disease NOS K84
K85 Elevatedbloodpressure
K86 Hypertensionuncomplicated
K87
K89 Transientcerebralischaemia
K90 Stroke/cerebrovascularaccident
K91 Cerebrovasculardisease
K92 Atherosclerosis/PVD
K93 Pulmonaryembolism
K94 Phlebitis/thrombophlebitis
K95 Varicoseveinsofleg
K96 Haemorrhoids

Musculoskeletal L

L01 Necksymptom/complain
L02 Backsymptom/complaint
L03 Lowbacksymptom/complaint
L04 Chestsymptom/complaint
L05 Flank/axillasymptom/complaint
L07 Jawsymptom/complaint
L08 Shouldersymptom/complaint
L09 Armsymptom/complaint
L10 Elbowsymptom/complaint
L11 Wristsymptom/complaint
L12 Hand/fingersymptom/complaint
L13 Hipsymptom/complaint
L14 Leg/thighsymptom/complaint
L15 Kneesymptom/complaint
L16
L18 Musclepain
L19 MusclesymptomNOS
L26 Fear of cancermusculoskeletal
L27 Fearmusculoskeletaldiseaseother
L28 Limited function/disability (l)
L29 Sympt/complt.Musculoskeletalother
L70 Infectionsmusculoskeletalsystem
L71 Malignant neoplasmmusculoskeletal
L72 Fracture:radius/ulna
L73 Fracture:tibia/fibula
L74 Fracture:hand/footbone
L75 Fracture:femur
L76 Fracture:other
L77 Sprain/strainofankle
L78 Sprain/strainofknee
L79 Sprain/strainofjointNOS
L81 InjurymusculoskeletalNOS
L82 Congenitalanomalymusculoskeletal
L83 Necksyndrome
L84 Back syndrome w/o radiatingpain
L85 Acquireddeformityofspine
L86 Backsyndrome withradiatingpain
L87 Bursitis/tendinitis/synovitisNOS
L88 Rheumatoid/seropositivearthritis
L89 Osteoarthrosis of hip
L90 Osteoarthrosis of knee
L91 Osteoarthrosisother
L92 Shouldersyndrome
L93 Tenniselbow
L94 Osteochondrosis
L95 Osteoporosis
L96 Acute internal damage knee
L97 Neoplasmbenign/unspecmusculo.
L98 Acquireddeformityoflimb
L99 Musculoskeletaldisease,other

Neurological N

N01 Headache
N03 Painface
N04 Restlesslegs
N05 Tinglingfingers/feet/toes
N06 Sensationdisturbanceother
N07 Convulsion/seizure
N08 Abnormalinvoluntarymovements
N16 Disturbanceofsmell/taste
N17 Vertigo/dizziness
N18
N26 Fearcancerneurologicalsystem
N27 Fearofneurologicaldiseaseother
N28 Limited function/disability (n)
N29 Neurologicalsymptom/complt.other
N70 Poliomyelitis
N71 Meningitis/encephalitis
N72 Tetanus
N73 Neurologicalinfectionother
N74 Malignantneoplasmnervoussystem
N75 Benign neoplasm nervous system
N76 Neoplasmnervoussystemunspec.
N79 Concussion
N80 Headinjuryother
N81 Injury nervous system other
N85 Congenitalanomalyneurological
N86 Multiplesclerosis
N87 Parkinsonism
N88 Epilepsy
N89 Migraine
N90 Clusterheadache
N91 Facialparalysis/bell'spalsy
N92 Trigeminalneuralgia
N93 Carpaltunnelsyndrome
N94 Peripheralneuritis/neuropathy
N95 Tensionheadache
N99 Neurological disease, other

Psychological P

P01 Feelinganxious/nervous/tense
P02 Acutestressreaction
P03 Feelingdepressed
P04 Feeling/behavingirritable/angry
P05 Senility,feeling/behavingold
P06 Sleepdisturbance
P07 Sexualdesirerereduced
P08 Sexual fulfilment reduced P09
P10 Stammering/stuttering/tic
P11 Eatingprobleminchild
P12 Bedwetting/enuresis
P13 Encopresis/boweltrainingproblem
P15 Chronicalcoholabuse
P16 Acute alcohol
P18 Medicationabuse
P19 Drugabuse
P20 Memorydisturbance
P22 Childbehavioursymptom/complaint
P23 Adolescentbehav.Symptom/complt.
P24 Specific learning problem
P27 Fearofmentaldisorder
P28 Limited function/disability (p)
P29 Psychologicalsymptom/compltother
P70 Dementia
P71 Organicpsychosisother
P72 Schizophrenia
P73 Affectivepsychosis
P74 Anxietydisorder/anxietystate
P75 Somatizationdisorder
P76 Depressivedisorder
P77 Suicide/suicideattempt
P78 Neuraesthenia/surmenage
P79 Phobia/compulsivedisorder
P80 Personalitydisorder
P81 Hyperkineticdisorder
P82 Post-traumaticstressdisorder
P85 Mentalretardation
P86 Anorexianervosa/bulimia
P98 PsychosisNOS/other
P99 Psychologicaldisorders,other

RespiratoryR

R01 Painrespiratorysystem
R02 Shortnessofbreath/dyspnoea
R03 Wheezing
R04 Breathing problem, other
R05 Cough
R06 Nosebleed/epistaxis
R07 Sneezing/nasalcongestion
R08 Nosesymptom/complaintother
R09 Sinussymptom/complaint
R21 Throatsymptom/complaint
R23 Voicesymptom/complaint
R24 Haemoptysis
R25 Sputum/phlegmabnormal
R26 Fearofcancerrespiratorysystem
R27 Fearofrespiratorydisease,other
R28 Limited function/disability (r)
R29 Respiratory symptom/complaintoth.
R71 Whoopingcough
R72 Strepthroat
R73 Boil/abscessnose
R74 Upperrespiratoryinfectionacute
R75 Sinusitisacute/chronic
R76 Tonsillitisacute
R77 Laryngitis/tracheitisacute
R78 Acutebronchitis/bronchiolitis
R79 Chronicbronchitis
R80 Influenza
R81 Pneumonia
R82 Pleurisy/pleuraleffusion
R83 Respiratoryinfectionother
R84 Malignantneoplasmbronchus/lung
R85 Malinant neoplasm respiratory, other
R86 Benign neoplasm respiratory
R87 Foreign body nose/larynx/bronch
R88 Injury respiratory other
R89 Congenitalanomalyrespiratory
R90 Hypertrophytonsils/adenoids
R92 Neoplasmsrespiratoryunspecified
R95 Chronic obstructive pulmonarydis
R96 Asthma
R97 Allergicrhinitis
R98 Hyperventilationsyndrome
R99 Respiratorydiseaseother

PROCESSCODES
SYMPTOMS/COMPLAINT
INFECTIONS
NEOPLASMS
INJURIES
CONGENITAL
OTHER DIAGNOSES

Skin S

S01 Pain/tendernessofskin
S02 Pruritus
S03 Warts
S04 Lump/swellinglocalized
S05 Lumps/swellingsgeneralized
S06 Rashlocalized
S07 Rashgeneralized
S08 Skincolourchange
S09 Infectedfinger/toe
S10 Boil/carbuncle
S11 Skininfectionpost-traumatic
S12 Insectbite/sting
S13 Animal/humanbite
S14 Burn/scald
S15 Foreign body in skin
S16 Bruise/contusion
S17 Abrasion/scratch/blister
S18 Laceration/cut
S19 Skininjuryother
S20 Corn/callosity
S21 Skin texture symptom/complaint
S22 Nailsymptom/complaint
S23 Hairloss/baldness
S24 Hair/scalpsymptom/complaint
S26 Fearofcancerofskin
S27 Fearofskindiseaseother
S28 Limited function/disability (s)
S29 Skin symptom/complaint other
S70 Herpeszoster
S71 Herpessimplex
S72 Scabies/otheracariasis
S73 Pediculosis/skininfestationother
S74 Dermatophytosis
S75 Moniliasis/candidiasisskin
S76 Skininfectionother
S77 Malignantneoplasmofskin
S78 Lipoma
S79 Neoplasmskinbenign/unspecified
S80 Solarkeratosis/sunburn
S81 Haemangioma/lymphangioma
S82 Naevus/mole
S83 Congenital skin anomaly other
S84 Impetigo
S85 Pilonidalcyst/fistula
S86 Dermatitisseborrhoeic
S87 Dermatitis/atopiceczema
S88
S90 Pityriasisrosea
S91 Psoriasis
S92 Sweatglanddisease
S93 Sebaceouscyst
S94 Ingrowingnail
S95 Molluscumcontagiosum
S96 Acne
S97 Chroniculcerskin
S98 Urticaria
S99 Skin disease, other

Endocrine/Metabolic and Nutritional T

T01 Excessivethirst
T02 Excessiveappetite
T03 Loss of appetite
T04 Feedingproblemofinfant/child
T05 Feedingproblemofadult
T07 Weightgain
T08
T11 Dehydration
T26 Fear of cancer of endocrine
T29 Endocrine/met./sympt/compltother
T70 Endocrineinfection
T71 Malignantneoplasmthyroid
T72 Benignneoplasmthyroid
T73 Neoplasmendocrineoth/unspecified
T78 Thyroglossalduct/cyst
T80 Congenitalanomendocrine/metab.
T81 Goitre
T82 Obesity
T83 Overweight
T85 Hyperthyroidism/thyrotoxicosis
T86 Hypothyroidism/myxoedema
T87 Hypoglycaemia
T89 Diabetes insulin dependent
T90 Diabetes non-insulin dependent
T91 Vitamin/nutritionaldeficiency
T92 Gout
T93 Lipiddisorder
T99 Endocrine/metab/nutrit.dis.other

Urological U

U01 Dysuria/painfulurination
U02 Urinaryfrequency/urgency
U04 Incontinenceurine
U05 Urinationproblemsother
U06 Haematuria
U07 Urinesymptom/complaintother
U08 Urinaryretention
U13 Bladder symptom/complaint other
U14 Kidneysymptom/complaint
U26 Fearofcancerofurinarysystem
U27 Fearofurinarydiseaseother
U28 Limitedfunction/disabilityurinary
U29 Urinary symptom/complaint other
U70 Pyelonephritis/pyelitis
U71 Cystitis/urinaryinfectionother
U72 Urethritis
U75 Malignantneoplasmofkidney
U76 Malignantneoplasmofbladder
U77 Malignantneoplasm urinary other
U78 Benignneoplasmurinarytract
U79 NeoplasmurinarytractNOS
U80 Injuryurinarytract
U85 Congenitalanomalyurinarytract
U88 Glomerulonephritis/nephrosis
U90 Orthostaticalbumin./proteinuria
U95 Urinarycalculus
U98 AbnormalurinetestNOS
U99 Urinary disease, other

Pregnancy, Childbearing, Family Planning W

W01 Questionofpregnancy
W02 Fearofpregnancy
W03 Antepartumbleeding
W05 Pregnancyvomiting/nausea
W10 Contraceptionpostcoital
W11 Contraceptionoral
W12 Contraceptionintrauterine
W13 Sterilization
W14 Contraceptionother
W15 Infertility/subfertility
W17 Post-partumbleeding
W18 Post-partumsymptom/complaintoth.
W19 Breast/lactationsymptom/complaint
W21 Concern bodyimageinpregnancy W27
Fear complications of pregnancy
W29 Pregnancy symptom/complaint other
W70 Puerperalinfection/sepsis
W71 Infectioncomplicatingpregnancy
W72 Malignantneoplasm relate topreg.
W73 Benign/unspec.neoplasm/pregnancy
W75 Injurycomplicatingpregnancy
W76 Congenital anomaly complicatepreg.
W78 Pregnancy
W79 Unwantedpregnancy
W80 Ectopicpregnancy
W81 Toxaemiaofpregnancy
W82 Abortionspontaneous
W83 Abortioninduced
W84 Pregnancyhighrisk
W85 Gestationaldiabetes
W90 Uncomplicate labour/delivery live
W91 Uncomplicate labour/delivery still
W92 Complicate labour/ deliverylivebirth
W93 Complicatelabour/deliverystillbirth
W94 Puerperalmastitis
W95 Breastdisorderinpregnancyother
W96 Complicationsofpuerperiumother
W99 Disorder pregnancy/delivery, other

FemaleGenitalX

X01 Genitalpainfemale
X02 Menstrualpain
X03 Intermenstrualpain
X04 Painfulintercoursefemale
X05 Menstruationabsent/scanty
X06 Menstruationexcessive
X07 Menstruationirregular/frequent
X08 Intermenstrualbleeding
X09 Premenstrualsymptom/complaint
X10 Postponement of menstruation
X11 Menopausalsymptom/complaint
X12 Postmenopausalbleeding
X13 Postcoitalbleeding
X14 Vaginaldischarge
X15 Vaginal symptom/complaint other
X16 Vulvalsymptom/complaint
X17 Pelvis symptom/complaint female
X18 Breastpainfemale
X19 Breast lump/mass female
X20 Nipple symptom/complaint female
X21 Breastsymptom/complt.femaleother
X22 Concern breast appearance female
X23 Fearsexuallytransmitteddisease(f)
X24
X26 Fearofbreastcancerfemale
X27 Feargenital/breastdiseaseother(f)
X29 Genitalsymptom/complt femaleoth.
X70 Syphilisfemale
X71 Gonorrhoeafemale
X72 Genitalcandidiasisfemale
X73 Genitaltrichomoniasisfemale
X74 Pelvicinflammatorydisease
X75 Malignantneoplasmcervix
X76 Malignantneoplasmbreastfemale
X77 Malignantneoplasmgenitalother(f)
X78 Fibromyomauterus
X79 Benignneoplasmbreastfemale X80 Benign neoplasm female genital X81 Genitalneoplasmoth/unspecied(f)
X82 Injurygenitalfemale
X83 Congenitalanomalygenitalfemale
X84 Vaginitis/vulvitisNOS
X85 CervicaldiseaseNOS
X86 Abnormalcervixsmear X87 Uterovaginalprolapse
X89 Premenstrualtensionsyndrome
X90 Genital herpes female
X91 Condylomataacuminatafemale
X92 Chlamydiainfectiongenital(f)
X99 Genital disease female, other

MaleGenitalY

Y01 Paininpenis
Y02 Painintestis/scrotum
Y03 Urethraldischarge
Y04 Penis symptom/complaint other
Y05 Scrotum/testissympt/complt.other
Y06 Prostatesymptom/complaint
Y07 ImpotenceNOS
Y08 Sexual functionsympt./complt.(m)
Y10 Infertility/subfertilitymale
Y13 Sterilizationmale
Y14 Family planning male other
Y16 Breastsymptom/complaintmale
Y24 Fearofsexualdysfunctionmale
Y25 Fear sexually transmitteddis.male
Y26 Fearofgenitalcancermale
Y27 Fearofgenitaldiseasemaleother
Y28 Limited function/disability (y)
Y29 Genitalsympt./complt.maleother
Y70 Syphilismale
Y71 Gonorrhoeamale
Y72 Genital herpes male
Y73 Prostatitis/seminalvesiculitis
Y74 Orchitis/epididymitis
Y75 Balanitis
Y76 Condylomataacuminatamale
Y77 Malignantneoplasmprostate
Y78 Malignneoplasmmalegenitalother
Y79 Benign/unspec. neoplasm gen. (m)
Y80 Injurymalegenital
Y81 Phimosis/redundantprepuce
Y82 Hypospadias
Y83 Undescendedtesticle
Y84 Congenitalgenl anomaly (m) other
Y85 Benignprostatichypertrophy
Y86 Hydrocoele
Y99 Genitaldiseasemale,other

Social Problems Z

Z01 Poverty/financialproblem
Z02 Food/waterproblem
Z03 Housing/neighbourhoodproblem
Z04 Socialculturalproblem
Z05 Workproblem
Z06 Unemploymentproblem
Z07 Educationproblem
Z08 Socialwelfareproblem
Z09 Legalproblem
Z10 Healthcaresystemproblem
Z11 Compliance/beingillproblem
Z12 Relationshipproblemwithpartner
Z13 Partner'sbehaviourproblem
Z14 Partner illness problem
Z15 Loss/deathofpartnerproblem
Z16 Relationshipproblemwithchild
Z18 Illness problem withchild
Z19 Loss/deathofchildproblem
Z20 Relationshipprob.parent/family
Z21 Behaviourproblemparent/family
Z22 Illnessproblemparent/family
Z23 Loss/deathparent/familymember
Z24 Relationshipproblemfriend
Z25 Assault/harmfuleventproblem
Z27 Fearofasocialproblem
Z28 Limited function/disability (z) Z29 SocialproblemNOS

Abbreviations

Anom ..... anomaly
behav. ..... behaviour
bronch. ..... bronchus
complicat.....complication
congen.....congenita
dis. ....disease
eval. evaluation
exam.examination
gen. genital
malig. malignant
metab. metabolic
musculo. musculoskeletal
NEC notelsewhereclassified
NOS nototherwisespecified nutrit. nutrition
oth other
preg. pregnancy
prob. problem
RFE reason for ncounter
sympt. symptom
unspec. unspecified
w with
w/o without