Barriers and Facilitators to Identifying and Treating Chronic Viral Hepatitis in Immigrants in Primary Care: the HepFREE Trial

Dr. Stuart Flanagan MB, Bch, BAO, MRCP

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

STATEMENT OF ORIGINALITY

I, Stuart Gordon Flanagan, 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.

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ABSTRACT

Chronic viral hepatitis, caused by Hepatitis B (HBV) or Hepatitis C (HCV) infection is a global public health concern, and contributes considerable health burdens from chronic liver disease, liver cirrhosis, hepatocellular carcinoma and death. The advent of new curative directly-acting antiviral drugs for HCV, and better treatment and management for HBV, offers an opportunity to improve outcomes for more than 300 million affected individuals.

In the UK approximately 0.4% of the population are infected with chronic HBV or chronic HCV, but prevalence is higher in immigrant populations.

Primary care can provide an important opportunity for case-finding infected individuals by offering testing to high-risk populations.

The HepFREE Trial: "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" reports on screening of immigrants in Bradford, London and Oxfordshire in the UK, and subsequent follow-up care.

In this thesis, I outline the background to viral hepatitis screening in primary care and the methodology of the HepFREE Trial. I analyse screening outcomes, disease staging and follow-up care of positive subjects, as well as qualitative research on the experience of healthcare professionals involved in trial delivery. I analyse a pre-screening survey exploring demographics, knowledge of viral hepatitis and treatment experience of a population of eligible individuals before the screening began.

I present current knowledge about viral hepatitis screening in primary care, the outcomes of a large multicentre national screening and follow-up trial, and the barriers and facilitators to screening as identified by healthcare providers and the high-risk patient population. I discuss my findings and how they contribute to our current understanding and future strategies for improvement of case-finding for viral hepatitis in primary care in the UK.

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List of Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
Anti-HBe	Antibodies to HBV e antigen
Anti-HBcAb	Antibodies to HBV core antigen
Anti-HCV	Antibodies to HCV
AST	Aspartate aminotransferase
APRI	AST to platelet ratio index
Au Ag	Australia antigen
BBV	Blood borne virus
cccDNA	Covalently closed circular deoxyribonucleic acid
CCG	Clinical commissioning group
CEG	Clinical effectiveness group
CI	Chief investigator
CMIA	Chemiluminescent microparticle immunoassay
CRF	Clinical research fellow
CSU	Commissioning support unit
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EASL	European association for the study of the liver
FBC	Full blood count
G1	Hepatitis C genotype 1
G1A	Hepatitis C genotype 1A
G1B	Hepatitis C genotype 1B
G2	Hepatitis C genotype 2
G3	Hepatitis C genotype 3
G3A	Hepatitis C genotype 3A
G3K	Hepatitis C genotype 3K
G4	Hepatitis C genotype 4
G5	Hepatitis C genotype 5
G6	Hepatitis C genotype 6
G7	Hepatitis C genotype 7
GP	General practitioner

HAV	Hepatitis A virus
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Healthcare professional
HCV	Hepatitis C virus
HDV	Hepatitis Delta virus
HEV	Hepatitis E virus
HICs	High income countries
HIV	Human immunodeficiency virus
ICC	Intracluster coefficient
IFN	Interferon
IL28b	Interleukin 28b
INR	International normalised ratio
IRAS	Integrated research application system
ISC	Indian sub-continent
KCH	Kings College Hospital
LFT	Liver function test
LMICs	Low-middle income countries
mRNA	Messenger ribonucleic acid
MSM	Men who have sex with men
NA	Nucleoside analogue
NHS	National health service
NICE	National institute for clinical excellence
NIH	National institute of health
NIHR	National institute for health and research
No.	Number
NS	Non-structural
NS3	Non-structural 3 protein
NS4A	Non-structural 4A protein
NS4B	Non-structural 4B protein

NS5A	Non-structural 5A protein
NS5B	Non-structural 5B protein
ODN	Operational delivery network
OR	Odds ratio
Peg-IFN	Pegylated interferon
PCR	Polymerase chain reaction
PCTU	Pragmatic clinical trials unit
PI	Principal investigator
PIS	Patient information sheet
PWID	Person who injects drugs
QALY	Quality Adjusted Life Years
QMUL	Queen Mary University of London
RLH	Royal London Hospital
RNA	Ribonucleic acid
S1	SystmOne
SIV	Site initiation visit
SVR	Sustained virological response
U&E	Urea and electrolytes
UK	United Kingdom
USS	Ultrasound scan
VHS	Viral hepatology specialist
VL	Viral load
WHO	World Health Organisation

List of units and symbols

IU/mL	International units per millilitre
IU/L	International units per litre
kPa	Kilo Pascals
>	More than
<	Less than

1. Introduction

1.1 Overview

Chronic Viral Hepatitis caused by infection with the Hepatitis B virus (HBV) or Hepatitis C virus (HCV) is an ongoing global public health concern, despite the advent of new curative directly-acting antiviral (DAA) therapies for HCV and protocols for the monitoring and suppression of HBV. Approximately 257 million people are infected with chronic HBV (1), and 71 million are infected with HCV (1) , with more than 1.34 million deaths in 2015 attributable to chronic active hepatitis, cirrhosis or primary liver cancer due to infection by these viruses (1).

Over the last two decades there has been a marked increase in morbidity and mortality due to viral liver disease. Low testing and diagnosis rates, as well as the poor efficacy and multiple adverse events associated with interferon based therapy, led to many individuals with chronic HBV and HCV infection progressing to advanced liver disease(2). However, access to new National Institute for Health and Care Excellence (NICE)-approved DAA therapies for HCV, along with better treatment and surveillance management for HBV, offers an opportunity to reduce end stage liver disease, hepatocellular carcinoma and mortality rates related to chronic infection with these viruses. With the development of highly efficacious DAA treatment, the focus for reducing morbidity and mortality from viral hepatitis is now on case-finding and engagement.

In the United Kingdom, seroprevalence studies in 2014-15 estimated 0.4% of the population are infected with chronic HBV (3) , and 0.4% infected with chronic HCV (2). Surveillance and research studies in England have found that of those screened for HCV, 2.2% of individuals of South Asian origin and 5.0% of eastern Europeans tested positive (2). However, there is a lack of robust, quantitative studies on identifying, testing and treating HBV and HCV among immigrant populations living in the UK (3).

Late diagnosis is major contributor to the mortality and morbidity caused by these viruses – 17% of HCV infections are diagnosed late (i.e. at a time of concurrent liver cirrhosis or hepatic decompensation within 12 months of diagnosis) (4). Early diagnosis provides an opportunity to prevent progression to liver fibrosis or cirrhosis and to test contacts and vaccinate those at risk of hepatitis B. Patients who are diagnosed late have often presented to healthcare professionals (HCPs) and have not been offered a viral hepatitis test on multiple opportunities (4).

Primary Care HCPs can play a key role in case-finding infected individuals. Screening of patients from high-risk groups has been shown to be cost-effective (5) and is estimated to be so in primary care settings (6) .The HepFREE Trial : “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" reports on screening of one high-risk group, immigrants who reside in Bradford, London and Oxfordshire in the UK, and the subsequent follow-up care of those who test positive in standard care versus primary care settings.

In this thesis, I outline the background to viral hepatitis screening in primary care and the methodology of the HepFREE Trial and describe my role in managing the trial in its final 3 years. I analyse screening outcomes, disease staging and follow-up care of those who tested positive.

My substudy "The HepFREE Provider Experience" is qualitative research on the experience of healthcare professionals involved in the provision of primary care screening for viral hepatitis.

I also analyse the pre-screening surveys of patients from the immigrant populations who were subsequently invited to participate in the HepFREE Study. These surveys explored demographics, knowledge of viral hepatitis and testing, vaccination and treatment experience of a population of eligible individuals before the screening was launched.

I discuss my findings in the context of current challenges in HBV and HCV care and future strategies for viral hepatitis case-finding in primary care. In this thesis I present the current knowledge about viral hepatitis screening in primary care, the outcomes of a large multicentre national screening and follow-up trial, and the barriers and facilitators to screening as identified by healthcare providers and the at-risk patient population. These findings contribute to our current understanding of how to improve case-finding for viral hepatitis in primary care in the UK.

1.2 Background

Approximately 257 million people are infected with HBV and 71 million with HCV worldwide (1). In the UK, approximately 175,000 people are living with HBV and 200,000 with HCV. Around 75% of these individuals are undiagnosed (2,7). Infection with HBV or HCV can lead to swelling and scarring (fibrosis) of the liver, which over time increases the risk of progression to liver cirrhosis and liver failure. Annual deaths from HCV have almost quadrupled in the last 20 years, in contrast to many other important chronic conditions (8). There is also a risk of communicating HBV or HCV to others, via mother-to-child transmission, sexual contact, and sharing of needles and injecting materials. As such the Lancet Commission launched the UK Liver Disease Crisis highlighting the importance of a joined-up approach to liver care. Three key points focussed on the role of primary care in improving the public's liver health: (i) improving expertise and facilities in primary care to strengthen detection of early disease and screening of high-risk patients in the community, (ii) eradication of chronic HCV from UK by 2030 and major reduction in the burden of HBV disease, (iii) increasing awareness of

liver disease in the general population and NHS. Improved screening programmes in primary care, more effective pathways to treatment and ensuring ongoing engagement with therapy should be the focus if we are to achieve a reversal in the current escalating rates of viral hepatitis disease (8).

To understand the challenges in meeting the goal of improving viral hepatitis care amongst immigrants in England, we must first understand the current background to viral hepatitis care.

1.3 Brief History of Hepatitis B and Hepatitis C Viruses

Although it was the 20th Century before molecular components of viral hepatitis were understood, "epidemic jaundice" was first described by Hippocrates in *De Morbus Internis* in 4th Century BC (9,10).

Hepatitis B Virus (HBV) is a blood-borne DNA virus which was first discovered in 1967 by Blumberg (11) although as early as 1908 viruses were proposed as having a causative role in liver disease (12). By the 1940s the existence of two hepatitis viruses had been posited – hepatitis A, transmitted by the faecal-oral route and hepatitis B, transmitted by blood (13).

In the late 1950s, Baruch Blumberg, an American physician and geneticist, began collecting multiple serum samples from various ethnicities around the world in order to understand the associations between disease, genetics and environment.

By the early 1960s, Blumberg and Anthony Allison, biochemist at the National Institute of Health (NIH) in the USA, developed agar gel diffusion techniques to detect novel polymorphisms (genetic variations). They focussed their studies on detecting the presence of a novel antigen-antibody complex which formed in samples from patients who had received multiple blood transfusions compared to those who had received none. The presence of this complex suggested that transfused patient's blood now contained antibodies previously exposed to protein polymorphisms in other transferred blood products. Blumberg and Allison reasoned that these polymorphisms may be antigenic. Therefore patients receiving multiple blood transfusions could develop antibodies against variants that they themselves had not inherited or acquired (11).

Harvey Alter, working at the NIH transfusion service, collaborated with Blumberg on agar gel diffusion testing samples from Blumberg's global collection and samples from patients who had received multiple blood transfusions.

One antibody found in a transfused haemophiliac patient reacted with the serum from a native Australian Aborigine. As the Aborigine's sample did not react with any other transfused samples this

raised the possibility that the rare reaction was due to infection rather than genetic variation. Testing the serum of the haemophiliac patient against thousands of other samples showed around 10% of samples from leukaemia patients reacted to the sample compared to 1 in 1000 non-haemophiliac blood donor samples. This new protein was named the "Australia" Au antigen.

At first Blumberg and Alter hypothesised that the Au antigen (Au Ag) increased the risk of developing leukaemia, and so tested for Au Ag in patients with Down's Syndrome (who have increased risk of developing leukaemia). Although Au Ag was found in up to one third of patient's with Down's, newborn babies from the same population tested negative compared to older children and adults housed in large institutions. Also, one young boy who had initially tested positive showed the presence of Au Ag when tested again a few months later. The boy was noted to have developed hepatitis at the time of repeat testing. On testing of further samples by Blumberg and other researchers in New York and Tokyo a clear link between the presence of the Au Ag in patients who developed hepatitis was made.

Subsequent isolation by electron microscopy and description of the whole virus in sera of patients testing positive for Au Ag, and in liver cells of patients with hepatitis by Dane et al led to the Au antigen as being renamed the Hepatitis B (transmission via blood) Surface antigen (HBsAg) (14). HBsAg became the marker of HBV infection.

The development of diagnostic markers for hepatitis A and B led to the recognition that some clearly infectious hepatitis was caused by another virus – originally named non-A, non-B hepatitis.

Hepatitis C virus (HCV) was first isolated as non-A non-B in 1989 by Choo et al (15) and found to be the cause of more than 90% of non-A non B hepatitis in the USA (16). Anti-HCV antibody is the marker of Hepatitis C infection, with further testing for HCV ribonucleic acid (RNA) as a marker of ongoing viral activity and chronic infection.

1.4 Viral Structure

1.4.1 HBV Structure

HBV is a hepadnavirus: a small enveloped-virus with double stranded circular deoxyribonucleic acid (DNA) (17). Replication is by reverse transcription: HBV virions deliver their DNA into hepatocytes at the time of infection (18). Viral DNA is then converted to covalently closed circular DNA (cccDNA). This serves as a transcriptional template for ribonucleic acid (RNA) and messenger RNA (mRNA) for HBsAg, HBV e Antigen and core antigen (HBeAg, HBcAg)(19). Multiple factors impact upon the clinical course of chronic HBV infection – these include host immune response, HBV viral strain and level of HBV DNA replication. In particular, age of acquisition is a key factor – the earlier the age of exposure, the more likely lifelong infection incurs (20). Presence of HBeAg is an indicator of active viral replication, and individuals with high levels (>10^7 IU/mL) of replicating HBV DNA are highly contagious (21).

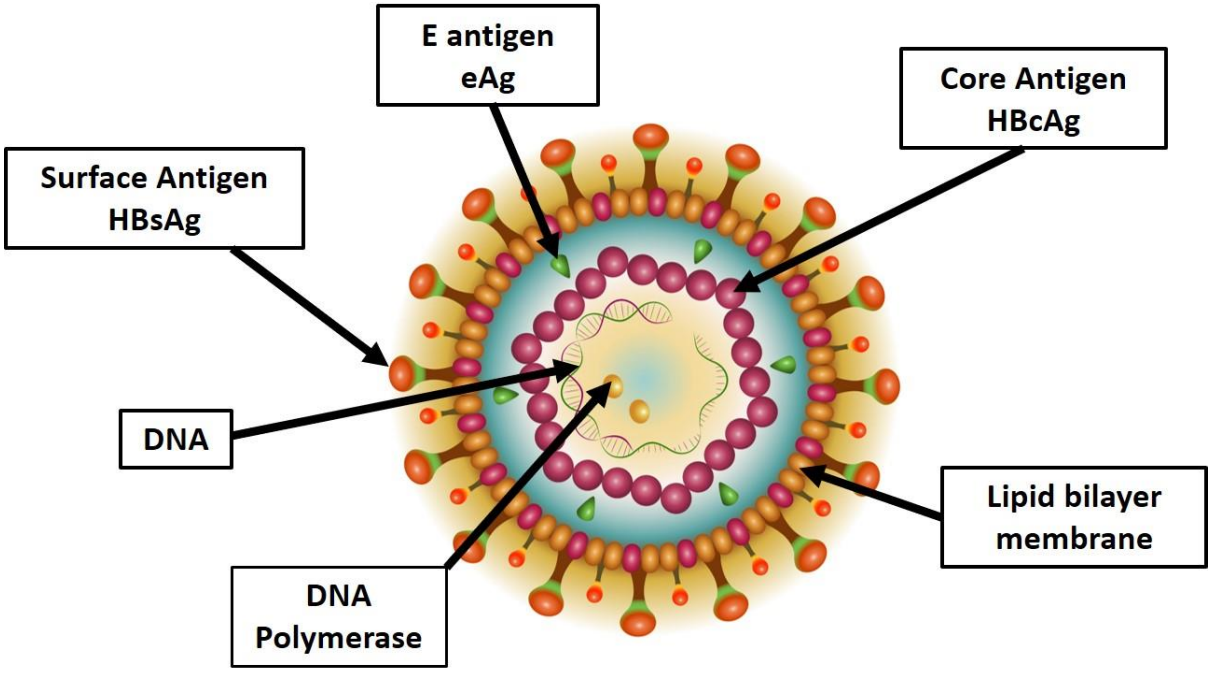

Figure 1: Hepatitis B virus structure

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1.4.2 HCV Structure

Hepatitis C virus (HCV) is an RNA virus belonging to the fabiviridae family (9). HCV is found in hepatocytic cytoplasm where it replicates at a rate of between 10^{10} to 10^{12} virions per day. Rapid viral replication is one of the reasons that the HCV genome mutates frequently, resulting in high genetic diversity characterised by regional variations in genotype prevalence (9).

Seven HCV genotypes have been described (known as Genotypes 1-7), with genotype 1 (G1) being the most common across the globe affecting 40% of those infected, and genotype 3 (G3) the second most common affecting around 30%, especially those born in South Asia (Pakistan, India, Bangladesh) (22).

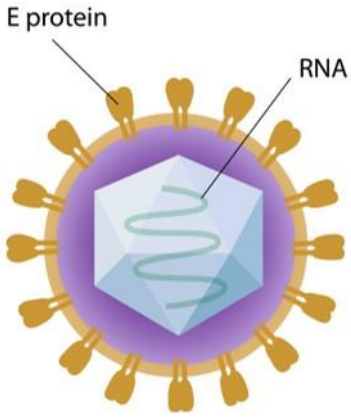

Figure 2: Hepatitis C virus structure

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1.5 Natural History of HBV Infection and HCV Infection

1.5.1 Natural History of HBV Infection

Acute Hepatitis B Infection

HBV replicates in hepatocytes, disrupting normal liver function. The subsequent immune response generates inflammatory damage in the liver tissue, leading to fibrosis, cirrhosis and in susceptible individuals may lead to development of Hepatocellular Carcinoma (HCC). (23)

The clinical course of Hepatitis B can be extremely variable and may be asymptomatic. During acute infection (within 6 months of exposure) patients may experience nausea, vomiting diarrhoea, jaundice and fever. The vast majority of adult patients will recover within 8 weeks and clear the virus, however up to 10% may become asymptomatic carriers (HBcAb positive) or develop chronic hepatitis B infection (23).

Chronic Hepatitis B

Chronic HBV infection is defined by WHO as 6 or more months of persistent HBsAg infection(23). The natural course of chronic HBV infection was, until 2017, divided into immune tolerance, immune clearance, immune control and immune escape phases. These phases have now been renamed HBeAg positive chronic infection, HBeAg positive chronic hepatitis, HBeAg negative chronic infection and HBeAg chronic hepatitis respectively, in order to better reflect pathological processes (21). All these phases are found in the HBsAg positive state and are dependent on clinical state and serological markers alanine aminotransferase (ALT) and HBV DNA levels to be identified. The highest risk of developing liver cirrhosis occurs in the immune clearance and immune escape phases indicating active viral replication which lead to liver necroinflammation and hepatocellular damage. Table 1 outlines the biochemical and virological findings in each of these disease states, and Box 1 outlines the natural history of HBV infection.

Risk of developing HCC is highest in patients with one or more factors that relate to the host (cirrhosis, chronic hepatic necroinflammation, older age, male sex, African origin, alcohol abuse, chronic co-infection with other hepatitis viruses or human immunodeficiency virus (HIV), diabetes or metabolic syndrome, active smoking, positive family history) and/or to HBV properties (high HBV DNA and/or HBsAg levels, specific mutations)(21) .

Table 1: HBV Chronic Infection Terminology EASL Guidelines 2017 (21)

	HBeAg Positive		HBeAg Negative	
	Chronic Infection	Chronic Hepatitis	Chronic Infection	Chronic Hepatitis
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2000 IU/mL*	>2000 IU/mL
Alanine Aminotransferase (ALT)	Normal	Elevated	Normal	Elevated*
Liver Disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune Tolerant	Immune Clearance	Inactive carrier	Immune Escape

EASL Guidelines Viral Hepatitis 2017 Table 1: Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers. *Persistently or intermittently. *HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patient without signs of chronic hepatitis.

Box 1 Natural History by chronology after HBV infection

1. Immune Tolerant Phase (now known as HBeAg Positive Chronic Infection)
   - HBeAg positive with high serum levels of HBV DNA.
   - Normal or minimally elevated ALT and normal liver histology and function.
   - These patients are highly contagious due to high levels of HBV DNA.
2. Immune Clearance (now known as HBeAg Positive Chronic Hepatitis)
   - Fluctuating but progressively increasing HBV DNA levels.
   - Increased ALT and histological activity.
   - Immune mediated histologic damage – increasing inflammatory hepatic necrosis.
3. Immune Control/ Inactive Carrier (now known as HBeAg Negative Chronic Infection)
   - Decrease in HBV DNA levels.
   - Inactive liver disease, with normal ALT.
   - No necroinflammation.
   - Inactive carrier state (for years or decades).
   - May be seen after spontaneous HBeAg seroconversion: the development of antibodies against the eAntigen.
   - When HBeAg cleared, HBeAb develops and HBV DNA is <2000 IU/mL.
   - Spontaneous seroconversion rate is 5-10% per year, although this varies among populations
4. Immune Escape (now known as HBeAg Negative Chronic Infection)
   - Reactivation of viral replication of mutated virions that do not express HBeAg, associated with high levels of HBV DNA and active necro-inflammation and progression to fibrosis. Progression to cirrhosis occurs at an annual rate of 2-5.5% (cumulative 5-year rate of progression of 8-20%). (24)

1.5.2 Natural History of HCV Infection

Acute Hepatitis C

Acute hepatitis C infection is usually asymptomatic or presents as a mild flu-like illness. Up to one third of patients may experience jaundice. The most common outcome in in 60-85% of cases is chronic HCV infection, detected by the persistence of HCV RNA after 6 months following infection. The range of resolution is largely based on retrospective studies of post-transfusion patients. Factors which can determine resolution or chronic infection include genetic factors (such as interleukin IL28b inheritance) immune response, gender, mode of acquisition, severity of acute illness, jaundice on presentation, immunosuppression, co-infection with HBV or HIV. (25) (26)

Chronic Hepatitis C

Chronic HCV infection is a leading cause of end-stage liver disease, hepatocellular carcinoma and liver-related death globally. The infection can cause persistent hepatocellular inflammation, leading to fibrosis and subsequent cirrhosis in at a rate of 10% per decade infected (26). HCV is an indolent infection with many individuals remaining asymptomatic until they present with end stage liver disease and its associated complications. The presence of cirrhosis also increases the risk of HCC to 1-5% per annum, with increased risk of liver failure and death. (25,26)

1.6 Impact of Chronic Viral Hepatitis on Morbidity and Mortality Risks

1.6.1 HBV Infection

The triggering of host and viral factors to end the HBeAg positive chronic infection phase, modulating the course of immune-clearance/inflammatory phase, HBeAg/HBsAg seroclearance and seroconversion, and even the occurrence of HBeAg-negative hepatitis flare are the key determinants to the life-long risk of liver injuries, liver cirrhosis and HCC (27).

The age at which HBeAg seroconversion occurs, and the severity of liver damage sustained during the HBeAg positive chronic infection phase are both important outcome determining factors during the natural course of chronic HBV infection (28).

There are two main age groups in which risk of HCC increases due to seroconversion: (i) very early HBeAg seroconversion in childhood (at < 3 years of age), along with severe liver damage, increases the risk of childhood HCC (29,30) (ii) delay in occurrence of HBeAg seroconversion until after the 4th decade of life is an important risk factor in developing HBeAg-negative hepatitis flare, liver cirrhosis, and HCC.(27)

Conversely, HBeAg seroconversion during childhood without severe liver damage is associated with a relatively uneventful course with a low viraemia profile, lower incidence of hepatitis reactivation after HBeAg seroconversion, and higher chance of spontaneous HBsAg seroconversion (28,31,32).

Wu et al have noted that earlier transition to HBeAg positive chronic hepatitis phase, and earlier HBeAg seroconversion in children with chronic HBV infection are both important predictors of spontaneous HBsAg seroconversion (31).

Chronic HBV has a significant impact on life expectancy: a US study showed that individuals who are infected with chronic HBV die on average 22 years earlier than those not infected, due to complications of liver cirrhosis, HCC and liver failure (33).

1.6.2 HCV Infection

Due to multiple confounders, cohort studies of heterogenous populations have not been able to fully clarify the natural history of chronic HCV infection. Development of cirrhosis in the context of hepatitis C infection is multi-factorial and risk factors for increasing the risks of fibrosis or cirrhosis include age at infection, male gender, alcohol consumption, obesity, insulin resistance, type 2 diabetes, co-infection with HBV or HIV, or immunosuppressive therapy (34).

Hepatitis infection can cause persistent hepatitis, but as the RNA viral genome in not integrated into the host, viral replication can be suppressed and cure achieved with virological treatment. Cure is defined as undetectable serum HCV RNA (known as sustained virological response) at 12 weeks following completion with treatment by Directly Acting Antiviral (DAAs) drugs (aka SVR12). For those treated with pegylated interferon and ribavirin, cure is defined as achieving SVR24, measured at 24 weeks following completion of therapy. (35,36).

Without treatment, HCV can persist in some individuals without causing abnormal liver function or change in biochemical markers such as a raised serum ALT. However these individuals can still progress to fibrosis, and will show a decline in ALT following curative treatment (37). This is a key consideration in who to test for the virus, as asymptomatic patients with apparently normal liver function tests may be still be infected with HCV and at risk of liver disease with the passing of time.

Approximately 16% of patients infected with chronic HCV will develop liver cirrhosis over a 20 year period (34), increasing to 41% by 30 years of infection. Rates of fibrosis progression are also related to the risk factors noted above such as alcohol, age and HBV or HIV co-infection.

1.7 Co-infection with other Blood-Borne Viruses

In those who are HBV infected, co-infection with Hepatitis Delta virus (HDV) can lead to rapid progression to liver fibrosis and cirrhosis (38). HDV is not an infective virus but is a satellite virus that can only lead to hepatitis in the presence of HBV infection. HDV is a single-stranded RNA genome in the deltaviridae family. It can be acquired either by co-infection or superinfection of individuals already infected with HBV. In a minority of individuals, co-infection will lead to a clearance of both viruses, however the majority of patients will develop chronic co-infection (9,38).

Co-infection with HBV-HDV leads to a more progressive course than monoinfection with HBV. Co-infected patients have a higher risk of earlier development of liver fibrosis and cirrhosis, and also an increased risk of hepatocellular carcinoma. (21).

Co-infection of HBV-HCV, and co-infection with HIV (e.g. HBV-HIV or HCV-HIV) also leads to a more progressive course than monoinfection with HBV or HCV. Co-infected patients are at higher risk of earlier development of liver fibrosis and cirrhosis (21,35,36).

1.8 Transmission

HBV transmission is via vertical (maternofetal), exposure to infected blood, and unprotected sexual intercourse. Individuals at risk of infections include those from high-prevalence countries, men who have sex with men (MSMs), people who inject drugs and healthcare workers (1).

HCV transmission is the same as HBV, and also includes anyone exposed to infected blood or in receipt of infected blood products prior to 1991, people who inject (or who have ever injected) drugs, individuals with tattoos or body piercings, and intra nasal cocaine users (1).

1.8.1 Immigrants as a particular At-Risk Population

More than 250 million people globally are estimated to be persistently infected with HBV, many of whom are from low and middle income countries (LMIC) in eastern Asia and sub-Saharan Africa. More than 1 million deaths occur each year due to chronic HBV infection. Approximately 2% per year of long-established chronic carriers terminate their active infection and become HBsAg-negative (1,7).

For chronic HCV infections there are large variations in estimates of prevalence across large global regions. The WHO Global Hepatitis report estimated chronic HCV infections at 71 million worldwide

(a lower figure than previous estimates), with the majority of infections occurring in the Eastern Mediterranean and Western Pacific regions (1).

At risk populations for HBV/HCV include anyone exposed to infected blood or receipt of infected blood products prior to 1991, people who inject (or who have ever injected) drugs, those born in higher prevalence countries, vertical (maternofetal transmission), men who have ever had sex with men, healthcare workers, dialysis patients, individuals with tattoos or body piercings, and intra nasal cocaine users.

Migrant populations are also more likely to be at risk of chronic viral hepatitis, particularly those from areas of known high prevalence (>2%) such as South East Asian (India, Pakistan, and Bangladesh), East Asia (China, Japan), Sub-Saharan Africa (Nigeria, Sierra Leone, and Somalia etc) and Eastern Europe (Poland, Romania etc). Appendix 2 includes the WHO's full list of high prevalence countries.

Patients from these LMICs may have been exposed to HBV and/or HCV at a young age due to mother-to-child transmission during pregnancy, poor infection control practices e.g. reusable or poorly sterilised vaccination needles, or shared use of razors. High prevalence in these areas had led to substantial morbidity, for example in West Africa where up to 15% of the population are chronic HBV infected (8) and Pakistan where HCV can exceed 20% in some regions (39).

In many high income countries (HICs) the overall prevalence is less than 1%, but remains high in the populations who were born abroad in a LMIC and migrated to the HIC (40–42). Amongst migrant populations in European countries, estimated HBsAg prevalence ranges from 1-15.4% (up to 6 times higher than the general population), and estimated HCV Ab prevalence ranging from 0-23.4% (up to 2 times higher than the general population) (43).

Screening for viral hepatitis in HICs has historically been informed by the risk behaviours of the local indigenous populations (such as injecting drug use, sexual risks) and not upon those within migrant populations, who are more likely to have been at risk of vertical transmission or vulnerable to healthcare exposure in their country of origin (44).

Screening for viral hepatitis in HICs may often neglect to offer appropriate testing to the migrant population, and migrants themselves may not prioritise testing. It has been shown that engagement with treatment following community based screening has been low (40).

1.9 Immunisations

1.9.1 HBV Immunisation

Subsequent to the discovery of HBV, development of sensitive tests and the screening of donor blood prior to transfusion led to a dramatic drop in post-transfusion hepatitis from the late 1970s onwards. An immunisation was developed based on HBsAg and is now one of the most widely used across the globe. Blumberg was awarded the Nobel Prize for Medicine in 1975 for his work in identifying HBV and developing an effective immunisation (11).

In the UK, immunisation has been recommended to specific at risk groups: injecting drug users, MSMs, commercial sex workers, close family or household contacts of an individual with chronic hepatitis B, families adopting or fostering children from countries with a high or intermediate prevalence of HBV, individuals receiving regular blood or blood products and their carers, patient with chronic renal failure, patients with chronic liver disease, individuals living with HIV, inmates of custodial institutions, individuals at occupational risks and those travelling to areas of high or intermediate prevalence (3). In August 2017, immunisation for all neonates was introduced as part of routine immunisations in the UK (45). Those who are not immunised, or do not mount an adequate immune response after vaccination but are subsequently identified as being at risk of recent exposure may be offered post-exposure prophylaxis with HBV immunoglobulin +/- immunisation.

1.9.2 HCV Vaccine Research

A vaccine for HCV has proved more elusive. With 6 known genotypes and more than 50 subtypes and frequent mutations, the search for a vaccine is has remained challenging. Phase I and Phase II human trials are currently in progress and development of prophylactic or therapeutic vaccine remains a priority (46).

1.10 Management and Treatment of Chronic Viral Hepatitis Infection

1.10.1 Assessment of Chronic HBV Disease in Primary Care

In the UK, the National Institute of Clinical Excellence (NICE) who publish guidelines on evidence-based best practice, have produced guidelines for the assessment and management of chronic HBV (47). Although specific UK guidelines for HCV have not yet been published, European guidelines have been issued. These have been combined in the section below.

Initial assessment of chronic HBV or HCV infection should include a full history and examination to identify risk factors for viral hepatitis and other causes of liver disease (including country of birth, alcohol and smoking history, history of recreational and injecting drug use, and family history of HCC).

Initial investigations for patients testing HBsAg positive should include serology for

- full blood count including platelets
- urea and electrolytes
- liver function tests including Alanine Aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), Bilirubin, Albumin, full globulins, prothrombin time and International Normalised ratio (INR)
- HBV specific tests (HBeAg, anti-HBE, anti-HBc IgM, HBV DNA levels)
- tests for co-infection with other BBVs such as HCV (anti-HCV), HDV (anti-HDV) and HIV (anti-HIV)
- and Hepatitis A Virus (HAV) immunity status.

For those testing HCV Antibody positive, serum HCV RNA should also be tested. The HCV RNA should be done as a reflex test at the local laboratory level – this will clarify whether the patient has active ongoing infection. A negative HCV RNA indicates that the virus has either been therapeutically cured or self-cleared. If the RNA test is positive the patient remains infected and the other serological tests should be completed.

NICE advise that all the above can be performed in primary care, and the results should be forwarded with a referral to a hepatologist, or to a gastroenterologist or infectious diseases specialist with an interest in hepatology. If the patient is a pregnant woman, she should be referred within 6 weeks of receiving the screening test result to allow treatment in the third trimester. Adults with decompensated liver disease should be referred immediately to a hepatologist or gastroenterologist with an interest in hepatology (47).

1.10.2 Assessment and Staging of Chronic Viral Hepatitis Disease in Secondary Care

In the secondary care setting, information about chronic HBV should be provided to patients and to family members or carers (if appropriate) before assessment. This information should include:

- the natural history of chronic hepatitis B / hepatitis C, including stages of disease and long-term prognosis
- lifestyle issues such as alcohol, diet and weight
- family planning
- monitoring
- routes of viral hepatitis transmission
- the benefits of antiviral treatment, including reduced risk of serious liver disease and death and reduced risk of transmission to others
- treatment options and contraindications based on the patient's circumstances
- causes of treatment failure, including non-adherence to prescribed medicines, and options for re-treatment
- Patients should be advised that their general practitioner should arrange testing and HBV immunisation (if appropriate) of sexual and household contacts.
- Patients should be offered HAV and/or HBV immunisation if appropriate.

As well as ensuring the initial serological investigations above have been completed, baseline imaging of the liver should include ultrasound scan (USS) liver and transient elastography (aka Fibroscan®) to assess for hepatocellular carcinoma and liver fibrosis stage respectively. Further investigation will be dependent upon this disease staging.

The staging of chronic Hepatitis B infection is dependent upon the natural chronology of HBV, various factors including age, ALT value, fibrosis score and the presence or absence of cirrhosis. Dependent on local guidelines, a liver biopsy may be indicated (see box 2 for further information). However biopsy is increasingly being superseded by non-invasive measures of cirrhotic change such as transient elastography.

Box 2 HBV Liver Biopsy Indicators

Transient elastography score below 6 kiloPascals (kPa)

Adults with a transient elastography score less than 6 kPa should be offered liver biopsy if they are < 30 years and have HBV DNA > 2000 IU/ml and abnormal ALT (greater than or equal to 30 IU/L for males and greater than or equal to 19 IU/L for females) on 2 consecutive tests conducted 3 months apart.

Adults with a transient elastography score less than 6 kPa are unlikely to have significant fibrosis, and should not be offered a liver biopsy if they have a normal ALT and HBV DNA <2000 IU/mL, as they are unlikely to have advanced liver disease or need antiviral treatment.

Transient elastography score between 6 and 10 kPa

Liver biopsy should be considered for adults with a transient elastography score between 6 -10 kPa to confirm the level of fibrosis, which cannot be accurately predicted in scores within this range.

In chronic HCV infection, the cumulative risk of cirrhosis after 20 years is approximately 16%, and rises to more than 40% at 30 years (34). Chronic Hepatitis C infection is disease staged as being either non-cirrhotic or cirrhotic dependent on findings from ultrasound scan, transient elastography or liver biopsy (21). Progression of fibrosis is non-linear however, and transition rates are highest at the F2-F3 progression (see section 1.9.3). Therefore identifying and treating patients at this progression is crucial in reducing risk of cirrhosis (34).

Dependent on local guidelines, HCV-related cirrhosis may be prioritised for treatment with DAA therapies.

1.10.3 Assessment of Liver Fibrosis and Cirrhosis

Historically, liver biopsy has been the gold-standard of investigation and staging of fibrosis/cirrhosis in liver disease. This is an invasive procedure whereby a skilled operator takes a percutaneous biopsy from the patient under local anaesthetic for histological examination. This procedure carries moderate risks including bleeding and haemorrhage, pain and discomfort during and after the

procedure, and is higher risk in those individuals who have liver cirrhosis and therefore poor control of clotting factors which may lead to significant bleeding (48).

The METAVIR score is a scoring system used to assess the extent of inflammation and fibrosis in chronic hepatitis C infection based on histopathological evaluation via biopsy (49). The METAVIR score is composed of a two-letter and two-number scoring system: A = histological activity (A0 = no activity, A1 = mild activity, A2 = moderate activity and A3 = severe activity) and F= fibrosis (F0 = no fibrosis, F1 = portal fibrosis without septa, F2= portal fibrosis with rare septa, F3 = numerous septa without cirrhosis and F4 = cirrhosis).

Over the past 10 years, there has been increasing use of transient elastography (aka Fibroscan®) a non-invasive shear wave technology to assess liver stiffness as a surrogate marker of the presence of liver fibrosis and cirrhosis (50). Vibrations of low amplitude and frequency are delivered by an ultrasound transducer probe and delivered through liver tissues. The resultant elastic shear wave propagates through the intrabdominal organ and it the probe measures its velocity. The velocity of the shear wave is directly related to tissue stiffness which correlates with fibrosis (51,52). This technique has the benefit of being more agreeable for patients than the liver biopsy procedure and offers a reliable non-invasive assessment of fibrosis stage equivalent to the METAVIR score which is independent of operator (49,51). Transient elastography detects significant fibrosis or cirrhosis with acceptable accuracy and offers incremental diagnostic value in detecting significant fibrosis, but not cirrhosis (53). Therefore it should be used as adjunct to serology and other imaging such as ultrasound if used in place of biopsy.

Fibroscanning® Procedure

The use of a Fibroscan® can be performed by a trained operator in an outpatient setting and is a straightforward and safe non-invasive test. The patient is asked to attend having fasted for 3-4 hours (to reduce the degree of liver stiffness caused by post-prandial blood flow). The patient lies on their left side with the right arm in maximal abduction. The probe is placed along a lower intercostal space to obtain a view of the right lobe of the liver (54–56). Once an area of at least 6 cm thick and free of large vascular structures or gallbladder has been identified, ten measurements are obtained using the Fibroscan® probe. A reliable exam should result in ten measurements with a 70% success rate, and the interquartile range should be less than 30% of the value of the median (54).

Table 2: Comparison of Transient Elastography and METAVIR scores with histological findings

Transient Elastography (Fibroscan®) Score	***METAVIR Score***	***Fibrosis Stage***	***Histological Findings***
1.5-7.4 kPa	*F0-F1*	*No or Mild Fibrosis*	*Indicates no or minimal liver fibrosis and no evidence of progressive liver disease*
7.5-9.4 kPa	*F2*	*Moderate Fibrosis*	*Indicates significant liver fibrosis and evidence of progressive liver disease*
9.5-12.4kPa	*F3*	*Severe Fibrosis*	*Indicates severe liver fibrosis and high-risk progression to cirrhosis*
>12.5kPa	*F4*	*Cirrhosis*	*Indicates extensive liver fibrosis consistent with cirrhosis*

1.11 Antiviral Treatment for Chronic HBV Infection

All major guidelines recommend pegylated interferon (PEG-IFN), or nucleoside analogues (NA) such as Entecavir or Tenofovir as first-line monotherapy in patients with chronic HBV (21,47,57). Choice of treatment is based on factors which include host, virus and drug-related considerations including duration of treatment, plans for pregnancy and potential side effects (58).

1.11.1 Interferon Monotherapy

Pegylated-interferon is a cytokine based immunomodulator which also has antiviral activity. It shows most benefit in the treatment of those with low HBV DNA levels and high ALT without advanced disease. Benefits include a finite duration of therapy, possible anti-HBe/antiHBs

seroconversion within 12 months and absence of resistance. However, it carries considerable adverse effects such as myalgia, fatigue, nausea, weight loss, bone marrow suppression and thyroid disease. It is delivered as a weekly injection which the patient can be taught to self-administer. It is contraindicated in pregnant women, those with a history of psychiatric illness, severe leucopoenia or thrombocytopenia and decompensated cirrhosis (21,59).

Desired treatment endpoints for interferon therapy in chronic HBV infection are defined as sustained serum HBV DNA < 2000 IU/mL, HBsAg loss together with ALT normalisation as well as HBeAg seroconversion in HBeAg positive patients (21).

1.11.2 Nucleoside Analogue Therapy

Entecavir and tenofovir (available as tenofovir disoproxil or the pro-drug tenofovir alafenamide) are NAs of the class nucleoside reverse transcriptase inhibitors (NRTI) which act by inhibiting HBV DNA polymerase. They are both delivered as oral tablets, taken once daily. Adverse events are rare and can include renal insufficiency and long-term use of tenofovir disoproxil (TDF) can lead to Fanconi's syndrome (hypophosphataemia and glycosuria) as well as decreased bone density. TDF should be dose adjusted according to creatinine clearance in patients with established renal disease (60–62). Both NRTIs have potent antiviral effects but the main disadvantages include lifelong therapy, and small risk of resistance if adherence if poor or intermittent.

The EASL 2017 antiviral treatment guidelines are summarised in Boxes 3, 4 and 5.

Box 3 When to Offer Antiviral Treatment for Chronic Hepatitis B (21)

1. Any Age / Disease Stage

- HBV DNA > 20, 000 IU/mL
- AND abnormal ALT (>30 IU/ml in males, >19 in females)

on 2 tests, 3 months apart

2. Adults with Cirrhosis and detectable HBV DNA

3. Co-Infection with HDV, HCV, or HIV

4. Age >30

- AND HBV DNA > 2000 IU/mL
- AND abnormal ALT (>30 IU/ml in males, >19 in females)

on 2 tests, 3 months apart

5. Age <30

- AND HBV DNA > 2000 IU/mL
- AND abnormal ALT (>30 IU/ml in males, >19 in females)

on 2 tests, 3 months apart

- AND evidence of necroinflammation or fibrosis on Liver biopsy, or TE score > 6kPa

Consider Treatment

- HBV DNA > 2000 IU/mL
- AND evidence of necroinflammation or fibrosis on Liver biopsy, or TE score > 6kPa

Box 4 HBV Treatment Options (21)

HBeAg-positive & HBeAg- Negative Chronic HBV

First Line: Pegylated-Interferon for 48 weeks

Contraindicated in Pregnancy

At 24 weeks if:

- HBV DNA decreased by less than 2 $\log_{10}$ IU/mL
- or if HBsAg >20,000 IU/mL

STOP & offer 2nd line treatment

Second Line:

Tenofovir Disoproxil if no HBeAg seroconversion, or relapse after PEG IFN

Entecavir, if Tenofovir contraindicated

Review adherence if detectable HBV DNA at 48 weeks

Add Lamivudine at 96 weeks if still detectable

If no cirrhosis – consider stopping at 12 months after HBeAg seroconversion

If HBeAg negative and no cirrhosis, consider stopping at 12 months after achieving undetectable HBV DNA AND HBsAg seroconversion

Box 5 Monitoring Chronic HBV (21)

Patients not on treatment:

- Immune Tolerant (HBeAg positive, active viral replication + normal ALT) → Monitor ALT every 24 weeks
    - Increase to every 12 weeks if ALT ↑
- Immune Control (HBeAg negative, normal ALT, HBV DNA <2000)→ monitor ALT and HBV DNA every 48 weeks or 12-24 weeks if cirrhosis

Patients on treatment:

Immune Tolerant Phase

ALT levels should be monitored every 24 weeks and increased to every 12 weeks if there is an increase in ALT levels.

Immune-control phase in Adults

ALT and HBV DNA levels should be monitored every 48 weeks

Consider more frequent monitoring (12-24 weeks) in patients with cirrhosis

1.12 Current Treatments for HCV

From the late 1990s until 2014, the mainstay of therapy for Hepatitis C treatment was a combination of injectable pegylated-interferon and oral ribavirin (a nucleoside analogue). This was an unsatisfactory treatment option for several reasons: the therapy achieved poor cure rates of 15-40% (63), both drugs are associated with multiple serious adverse effects (such as pancytopenia, abnormal thyroid function tests, associated psychiatric disorders) and required up to 72 weeks of twice daily oral therapy and weekly injections (59,64).

In the early 2010s, the development of directly acting antivirals (DAAs) revolutionised hepatitis c therapies as they are oral short duration (either 8, 12 or 16 weeks once daily) medication which provide cure rates of more 95% and highly tolerable by most patients. Ongoing studies have also shown DAAs are highly efficacious in patients who have failed on previous non-DAA therapies, or who have cirrhosis at the time of treatment (65–74).

Current DAAs are derived from three main classes:

- NS3/4A Inhibitors (e.g. Paritaprevir)
- NS5A Inhibitors (e.g. Ledipasvir)
- NS5B Inhibitors (e.g. Sofosbuvir)

Newer generation therapies are now pangenotypic and can be used without prior knowledge of viral genotype (73,74) .

1.13 Surveillance for Hepatocellular Carcinoma in adults with Viral Hepatitis Infection

6-monthly surveillance for hepatocellular carcinoma by hepatic ultrasound and alpha-fetoprotein serology testing should be performed for patients with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or cirrhosis.

In HBV-infected without significant fibrosis or cirrhosis, 6-monthly surveillance for HCC should be considered if the person is older than 40 years and has a family history of hepatocellular carcinoma and HBV DNA greater than or equal to 20,000 IU/ml (21).

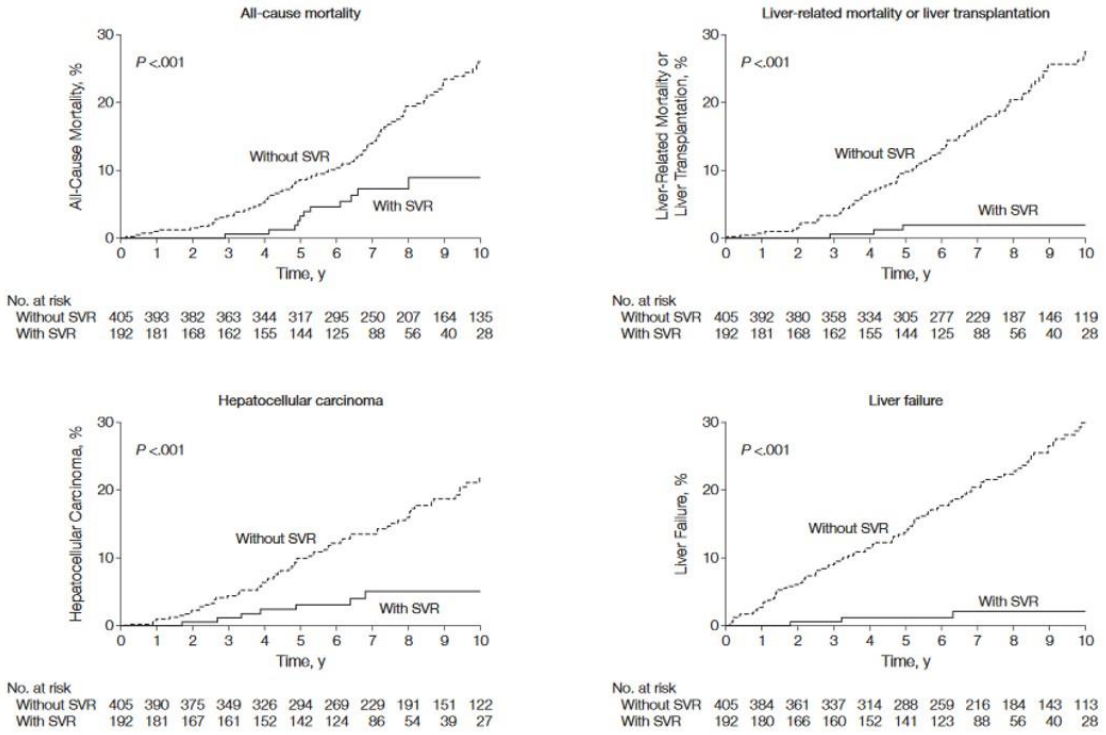
Patients who have been successfully cured of HCV infection only require ongoing 6-monthly HCC surveillance if they were noted to have cirrhosis prior to treatment initiation (36).

1.14 Benefits of Achieving Viral Suppression

Suppression of HBV replication with oral NRTIs prevents complications improves outcomes and can also reverse cirrhosis (75,76).

The health benefits of achieving SVR has been documented in both the Interferon treatment era (77) and the DAA era (78). The vast majority of HCV-infected patients will see an improvement in fibrosis and necro-inflammation scores and also a reduction in all-cause mortality outcomes as well as likelihood of liver-related mortality and morbidity and progression to liver transplant (see figure 3).

Figure 3: Outcomes for All-Cause Mortality, Liver-associated mortality, Hepatocellular carcinoma and Liver failure in those achieving SVR and those not achieving SVR (78)



1.15 Access to Viral Hepatitis Treatments amongst the Migrant Population

1.15.1 Limited Access to Treatments

As discussed earlier, many migrants from LMIC who have migrated to HICs carry a higher risk of viral hepatitis and have been identified as at-risk populations. Despite the NICE, EASL and WHO Guidelines regarding testing at-risk populations, access to treatment for HBV and HCV infected patients remains limited (79).

Multiple retrospective studies have highlighted the undertreatment of patients in various settings. Giannini et al followed a cohort of 363 patients chronically monoinfected with HBV for at least 1 year in tertiary referral centres. After 12 months, 84% potential treatment candidates (41 of 49 patients) were not treated, despite having elevated serum HBV DNA (>20,000 IU/mL) or being HBeAg positive with an elevated HBV DNA. Although there were limitations to this study such as a lack of uniform serum ALT work-up, low rate of disease staging (by imaging or biopsy) and no measurement of patients refusal of treatment, it does underline that even patients with chronic infection in specialist care may not receive timely therapy (80).

In a 2010 US study, 84% of low-income and immigrant patients with HBV infection who were followed in a publicly-funded health-care system did not receive HBV treatment between 1994 and 2006. Interestingly, in this study the strongest predictor of treatment was HBV-HIV co-infection, due to dual effect of NRTIs and use of tenofovir to treat both infections. When HIV-HBV co-infected patients were removed from the results, 90% of HBV mono-infected patients were not on treatment, and therefore at a disadvantage compared to co-infected patients. One of the documented reasons for nontreatment was that only 28% of had HBeAg and HBV DNA serology, highlighting the importance of serological markers in disease staging. However, barriers to treatment were rarely documented. (81)

Other studies suggest underdiagnosis could lead to up to half of eligible HBV patients not being offered treatment. (82,83) HCV infection has historically been underdiagnosed and undertreated: in 2004, of the total UK population that had been infected with hepatitis C, only 19% had been diagnosed and less than 10% of those went on to receive treatment. (84)

The consequences of delayed treatment for chronic HBV and HCV infection increases health burden to these patients, and financial burden to the wider community.

1.15.2 Barriers to Care

Possible barriers to high risk immigrant populations accessing treatment were explored in a USA 2011 review (79). These were grouped into Personal and Environmental barriers:

Personal barriers were noted to be:

- lack of information or misinformation about the disease;
- cultural beliefs regarding physician usage when not feeling ill;
- fear of stigmatization and discrimination by family, friends and community members
- HBV knowledge deficits regarding transmission, prevention, diagnosis and treatment outcomes of HBV

Environmental Barriers:

Some of these were specific to the US healthcare system. But provider barriers can also occur in any healthcare setting. The authors noted the following issues:

- lack of access to routine, ongoing medical care because of lack of insurance or being under-insured
- provider-related barriers: providers are often unaware of the risk groups that should be screened for HBV, or there is a communication breakdown with high-risk individuals that stems from language and cultural barriers, especially with foreign-born persons from endemic regions.

1.16 Screening for Viral Hepatitis

Although there are screening recommendations for viral hepatitis testing, there is no formal screening programme in the UK. This is even though HBV and HCV infections fit the Wilson and Junger criteria for a screening programme (85), which are:

- The condition is an important problem with a natural history characterised by a latent or early symptomatic stage
- There is a suitable acceptable diagnostic test
- There is accepted an established treatment
- Case-finding is cost-effective.

Screening for viral hepatitis has been shown to improve outcomes and be cost-effective (5). A 2010 Dutch study used a Markov chain statistical model (describing a sequence of events where the probability of each event is dependent on the state attained by the previous event) to assess the cost and health outcomes of a cohort of HBV-infected individuals in the Netherlands. For a one-off screening test, liver-related mortality was reduced by 10% and the intervention was found to be cost effective. However, this assumed patients would be more likely to attend a specialist appointment after participating in a screening programme rather than being opportunistically tested, and that they would be offered treatment if they were eligible (which as has been discussed above is not always the case). A 2015 systematic review of the cost-effectiveness of HBV and HCV screening noted that the arrival of DAAs has considerably changed the landscape in making HCV screening cost-effective, even with the higher costs of the new drugs (86), supporting earlier findings (87).

1.16.1 Prevalence of Viral Hepatitis amongst immigrants outside of the UK

Several European studies have investigated the prevalence of viral hepatitis amongst migrants to HIC outside of the UK. In Malta, 500 asylum seeking migrants were tested for HBsAg and HCV Ab (as well as being tested for Tuberculosis and syphilis). 83.2% of participants were from Somalia, with the rest from Eritrea (8.2%), Ethiopia (2.4%) and Western Africa countries (5.6%). HBsAg was positive in 31 subjects (6.1%) and HCV Ab positive in 3 (0.6%). (88)

Several Dutch studies have looked at the prevalence of viral hepatitis in immigrant populations. A wide-ranging retrospective study looked at the prevalence of viral hepatitis in 4 surveys in Amsterdam (i) 3895 heterosexual visitors at STI clinics (ii) random samples of 4563 pregnant women (iii) 1309 inhabitants of Amsterdam (iv) population-based random sample of 4428 people living in the Netherlands. In total 4860/14,195 (34%) of subjects were non-Western. Overall HCV Ab seroprevalence was low (0.3-0.6%). First-generation non-Western immigrants were up to five times more likely to be HCV-positive (0.7-2.3%) than Western participants (0.1-0.4%). Except for survey 3, second-generation non-Western immigrants had a lower HCV prevalence than first-generation immigrants, comparable to Western migrants and the Dutch population. Phylogenetic analysis showed that the majority of the HCV-positive, first-generation non-Western non-European immigrants were infected with endemic strains which are rarely observed in Europe. (89)

Another Dutch study looked at the prevalence of HCV Ab and RNA amongst 465 first generation Egyptian migrants (from a country of known high HCV prevalence) to the Netherlands. 11 (2.4%) participants had HCV Ab, 10 of whom were HCV RNA positive. HBsAg prevalence was 1.1%. Most

(9/10 HCV; 3/5 HBV) chronic infections were newly diagnosed. (90) A further Dutch study based in Arnhem tested 709 first generation migrants of Turkish origin for HBsAg and HCV Ab. 3.0% were HBsAg positive and 0.4% HCV Ab positive. (91)

In Finland, a random sample of 3000 migrants from Kurdish, Russian or Somali origin who had lived in Finland for at least one year were invited to test for HBV, HCV, syphilis and HIV. Seroprevalence of hepatitis B surface antigen (HBsAg) was 2.3%, hepatitis C antibodies 1.7%. Among the Somali population (n = 261), prevalence of previously undiagnosed chronic hepatitis B diagnosis was 3.0%. (92)

Outside of Europe, a large Chinese study tested 17,377 (95% of whom were Han Chinese ethnicity) migrant workers who had moved location within the country. The prevalence of HCV infections was 0.40% (95%CI: 0.31%-0.51%). (93)

A meta-analysis of 50 studies collated from four electronic databases representing 38,635 immigrants looked at the prevalence of HCV Ab. Overall HCV Ab prevalence was 1.9% (95% CI 1.42-2.7%). Older age and region of origin, particularly Sub-Saharan Africa, Asia, and Eastern Europe were the strongest predictors of HCV seroprevalence. The estimated HCV seroprevalence of immigrants from these regions was >2% and higher than that reported for most host populations.(94)

1.16.2 Prevalence of Viral Hepatitis amongst immigrants to the UK

In the UK, although several studies have looked at HBV and HCV prevalence amongst higher risk groups including people who inject drugs (PWIDs), Homeless persons and men who have sex with men (MSMs)(95–97), fewer studies have investigated prevalence amongst migrants to the UK. Testing for viral hepatitis may be part of wider infectious disease screening for at-risk patients. In the UK, over 80% of cases of tuberculosis are non-UK born (98), , a migrant population that is also at risk of viral hepatitis. Between 2008-2011, Nooredinvand et al investigated the prevalence of chronic HBV and HCV in 429 newly diagnosed Tuberculosis patients (both active and latent TB) attending a tertiary care centre (St Mary's Hospital, Imperial College Healthcare Trust) in central North West London. Patients were tested for for HBcAg, HBsAg, HCV IgG antibody and HIV antibody. Prevalence of HBsAg was 2.6%, and 1.6% were HCV Ab positive. The prevalence of chronic HBV or HCV in this predominantly migrant population was significantly higher than the estimated United Kingdom prevalence of 0.3% for each. (99) In 2009, Uddin et al undertook community-based testing at five sites in England. (40) A total of 4998 people attending community centres were screened for viral hepatitis using oral fluid testing. The overall prevalence of anti-hepatitis C virus (HCV) in people

of south Asian origin was 1.6% but varied by country of birth being 0.4%, 0.2%, 0.6% and 2.7% in people of this ethnic group born in the UK, India, Bangladesh and Pakistan, respectively. The prevalence of HBsAg was 1.2%-0.2%, 0.1%, 1.5% and 1.8% in people of this ethnic group born in the UK, India, Bangladesh and Pakistan, respectively. The increased prevalence in subjects from Pakistan (compared with those originally from the UK, and also those from other parts of South Asia) noted in this study indicated that prevalence cannot by easily predicted from ethnicity and country of birth. This study laid ground for the HepFREE trial proposal. See Table 3 for a full summary of all these trial findings.

Table 3: Prevalence Outcomes of Viral Hepatitis Migrant Screening Studies

Authors and Reference	Year	Location	Total Screened	Migrant Country of Origin	HBV Test	HCV Test	Prevalence HBV (%)	Prevalence HCV (%)
Padovese et al (88)	2014	Malta	500	Somalia (83%) Eritrea (8%) Ethiopia (2.4%) Other West Africa (5.6%)	HBsAg	HCV Ab	6.1%	0.6%
Urbanus et al (89)	2011	Netherlands	4428	Surinam Turkey Morocco Other Non-Western	----	HCV RNA	----	1.6% 0% 2.3% 1.6%
Zuure et al (90)	2013	Netherlands	465	Egypt	HBsAg	HCV Ab and HCV RNA	1.1%	2.36% HCV Ab positive, 2.15% RNA positive
Richter et al (91)	2012	Netherlands	647	Turkey	HBsAg	HCV Ab	3.0%	0.4%
Tiittala et al (92)	2018	Finland	3000	Kurdish (33.3%) Russia (33.3%) Somalia (33.3%)	HBsAg	HCV Ab	2.3%	1.7%
Pan et al (93)	2013	China	17.377	Chinese Migrant Workers	----	HCV Ab	----	0.4%
Greenaway et al (94)	2015	Metanalysis	38,635	All World Regions	----	HCV Ab	----	1.91% (1.35-2.69%)
Uddin et al (40)	2009	UK	4998	India Bangladesh Pakistan	----	HCV Ab	----	0.2% 0.6% 2.7%
Noorendinvand et al (99)	2008-2011	UK	429	Non-UK (92.5%) UK (7.5%)	HBsAg	HCV Ab	2.6%	1.6%

1.17 Screening for Viral Hepatitis in Primary Care

Screening for viral hepatitis has been trialled in various secondary care settings such as Emergency Departments (100–104) and outpatients colonoscopy services (105,106). In sub-Saharan Africa, community healthcare services have provided testing opportunities for HBV and HCV. (107)

Primary Care has an important role in providing screening for many national programmes such as cervical cancer (108) and bowel cancer (109). There has been an increasing interest in the opportunity to use general practice as a location for viral hepatitis testing, particularly as general practitioners (GP)s may already be offering the tests as part of a panel of liver investigations, or as part of antenatal care.

NICE has provided guidance on screening for viral hepatitis in primary care for targeted groups, but implementation is not uniform at a national level (3). High prevalence of hepatitis markers have been detected in immigrant populations in Germany (110) and in the UK (111,112), particularly those originally from countries of known high prevalence, likely due to poor infection control practices e.g. mother-to-child transmission, reusable needles for vaccination, shared use of barbers' razors in countries of origin. Case finding of both HBV and HCV in at risk populations is cost-effective (5) and this is estimated to be the case in primary care settings (6). General Practitioners and primary care health professionals can play an important role in finding infected individuals and ensuring they are part of a care pathway which offers cure or surveillance. Closing the gap between the diagnosed and undiagnosed remains one of the major challenges in viral hepatitis care (113) and primary care offers an opportunity to recognise viral hepatitis risks in order to offer targeted screening. Migrant populations may face potential barriers to screening, such as stigma related to viral hepatitis infection, language barriers, and poor knowledge of the effects of chronic hepatitis B & C. Most infected individuals will be asymptomatic and may also have normal liver function tests, making their identification difficult for non-specialist clinicians (114).

Implementation of primary care screening programmes has shown an increase in case-finding and linkage to care in the US and Europe (115,116) but as yet such strategies are not yet standard practice in the UK. A brief risk screener with a clinical reminder has been shown to be effective in increasing HCV screening rates in primary care (117).

A review of 2988 cases of viral hepatitis from 12 EU countries showed that the most common reported place of testing was general practice (26.9%), with 35.6% of chronic cases being detected via this source. (118)

General Practice Trends in 2015 (119) reports that 57,170,000 patients are registered to a primary care practice in the England, with an average 7,183 patients at each practice. This presents an excellent opportunity for a wide range of patients to be invited for testing, including those from migrant populations who are asymptomatic and have normal liver function.

Areas of denser migrant populations are more likely to have a higher prevalence of viral hepatitis and therefore primary care in urban settings has been the focus of numerous case-finding initiatives.

As part of the EU funded project "HEPScreen" in 2015, an online survey amongst GPs was conducted across 6 EU countries (the UK, Germany, the Netherlands, Hungary, Italy and Spain) to assess how commonly risk groups are offered a viral hepatitis test (120).

Five to ten GPs were surveyed in each country (except for Hungary n=1 and Germany n=4). In the majority of cases, immigrants were variably or not routinely screened for HBV/HCV, although routine testing was offered to PWIDs. Testing for HBV amongst MSMs was common practice in the UK, but HCV testing was only occasionally offered to this group. More than 44% of GPs in all countries (except Hungary) offered routine viral hepatitis screening to patients living with HIV. GPs were unlikely to monitor clinical outcomes (apart from side effects) in patients undergoing treatment.

In addition to the testing survey, knowledge of viral hepatitis guidelines amongst healthcare professionals was also assessed (121). Of 268 respondents, 80% were aware of the HBV guidelines, and 73% aware of the HCV guidelines in their countries.

The role of GPs involved in the management of chronically infected patients was not clear to the professional groups surveyed, and raising awareness of viral hepatitis disease amongst GP was recommended for more effective implementation of testing guidelines. These guidelines should be specifically designed for and actively promoted among those who follow them and accompanied by diverse training for different professional groups.

In order to improve the offering of viral hepatitis tests to at risk groups, an Australian study implemented four interventions during a 15 month period at a primary care practice with approximately 3000 registered patients. The interventions were: staff education, quality improvement (audit and feedback), review of electronic records to assess HBV risks and patient-triggered activities (a reminder card for each consultation). Although the interventions increased testing rates by 60% (up from 15 to 24 tests per month), the proportion of patients from Africa and Asia testing did not increase. (122)

1.18 Keeping patients engaged in care

Testing for viral hepatitis in Primary Care is one part of an ongoing continuum care of care, which starts with a serology test. The second stage after a positive result is confirmation testing and disease staging (continuing care), with the third stage being treatment or monitoring in the context of chronic infection. Patients (especially those from migrant populations) may be lost at each stage, highlighting the need to raise awareness amongst both healthcare professionals providing the care and at-risk populations (123).

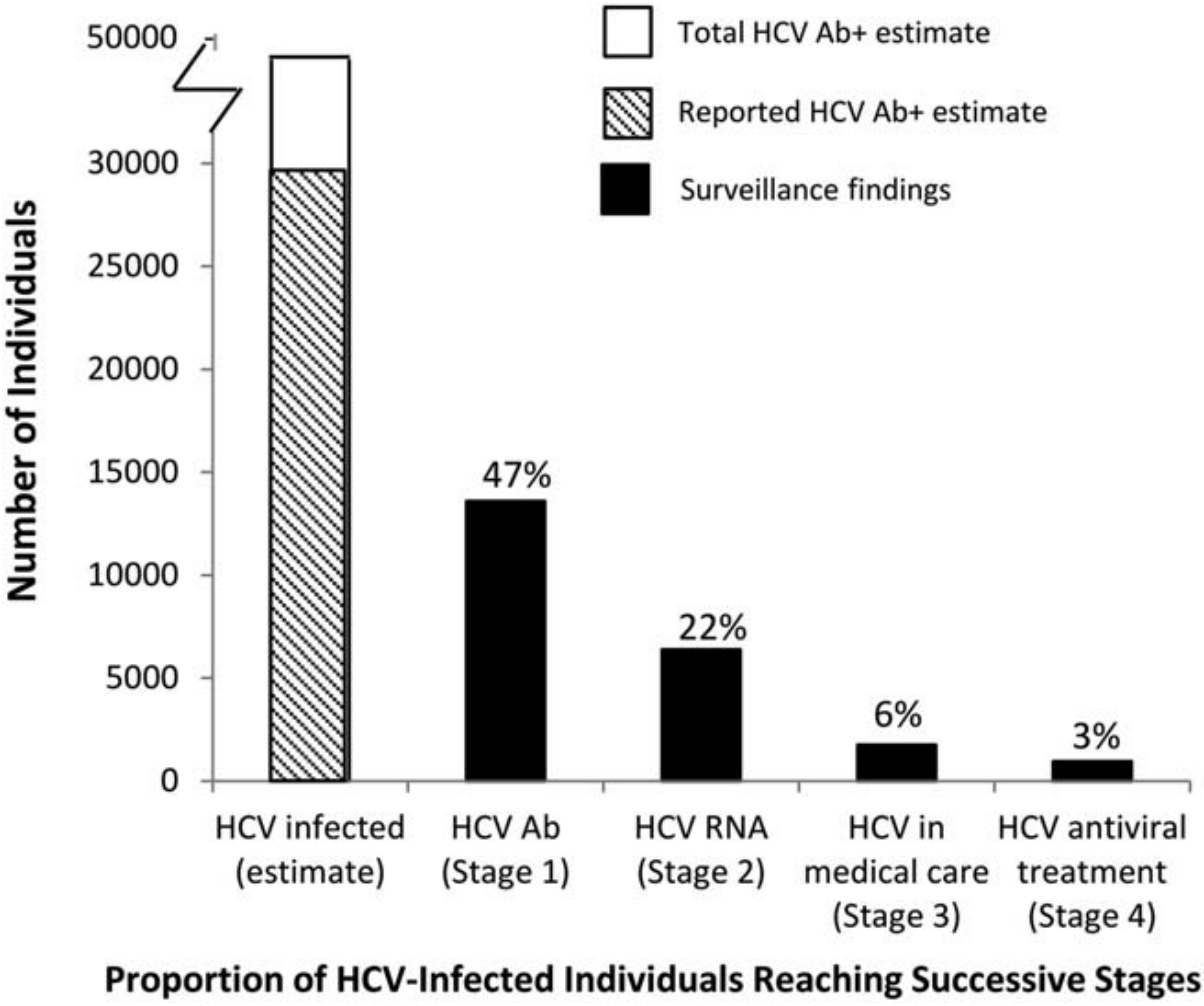
A study looking at the outcomes for the various stages of the care continuum for HCV infection in Philadelphia, USA between 2010-2013 estimated 2.9% of the adult population would be HCV Ab positive (47,525 / 1,585,848) based on seroprevalence studies (123).

During the study period the Health Department received HCV test results for 28,990 unique individuals, 13,596 (47%) of which were HCV Ab positive and 6,383 (22% of total) were HCV RNA positive. Of those in whom disease was confirmed, only 1,745 (6% of estimated total morbidity) were in care – defined as two tests within 6 months or a test ordered by a specialist. 956 (3% of total) were, by 2013, estimated to have received or were currently receiving HCV therapy.

Recommendation of offering a one-off HCV Ab test to all US patients born between 1945-1965 (the "baby-boomers") was made in September 2012 and a significantly higher number of individuals received their first positive HCV test in the months after this ($p<0.001$).

Figure 4 shows the engagement of patients in the HCV care continuum at each stage. In addition, it was noted that older (>40 years) male patients were more likely to remain engaged through to stage 4 of the continuum. Race and ethnicity was not available for all patients, but for those in which it was recorded, 45% of patients in stage 4 were recorded as Black ethnicity.

Figure 4 The continuum of hepatitis C testing, referral to care and treatment in Philadelphia from January 2010 to December 2013 (123)



1.19 Delivering Care

Although there has been a drive to expand viral hepatitis screening and case-finding in primary care as noted above, the role of the general practice in delivering care is less understood. With the opportunity to offer patients all oral therapy for a short, fixed time period, many primary care providers who see multiple patients with HCV could provide curative therapy in an environment where patients are potentially less likely to default from care (124). Community based clinics have been a mainstay of HCV service delivery for PWIDs but these are usually not related to primary care providers, and the same model has not been trialled for other at-risk groups. (125,126)

Challenges in providing a primary care-based model include whether general practitioners have the skills to manage viral hepatitis and also whether the primary care surgery is equipped with appropriate staff skillsets and tools to function as a setting for viral hepatitis care.

A US survey in 2001 was amongst the first to assess the knowledge base and practice patterns of primary care physicians in the era of interferon-based therapies (127).

4000 primary care physicians in the US were surveyed to assess knowledge of risk factors for HCV, management of HCV patients and attitudes towards HCV testing. 1412 (39%) responded and the vast majority (>90%) correctly identified common risk factors for HCV. 59% reported asking all patients about HCV risk factors, and 70% reported testing those with risk factors for HCV. 78% tested all patients with elevated liver enzymes for HCV infection. At the time of the survey, 72% of US GPs referred HCV-positive patients with elevated liver enzyme patients to specialists but only 28% would refer HCV-positive patients with normal liver function. 25% reported that they did not know what treatment to recommend for HCV.

Recruiting and training GPs to provide treatment for HCV could be a key component in the eradication of the virus. (128) One non-randomised, open-label US study in 2015 assigned 600 HCV RNA positive patients to receive treatment at either (i) Nurse Practitioner, (ii) Primary Care Physician or (iii) Specialist, who had all received uniform training prior to the trial. 96% of patients were black, 69% male, 72% had HCV G1 infection 1a infection and 20% had cirrhosis. 82% of patients were treatment naïve. All patients were treated with ledipasvir-sofosbuvir, with the outcome of the study being achievement of SVR. 516 patients achieved SVR, a response rate of 86% (95% CI, 83.0% to 88.7%), with no major safety signals. Response rates were consistent across the 3 provider types: NPs, 89.3% (CI, 83.3% to 93.8%); PCPs, 86.9% (CI, 80.6% to 91.7%); and specialists, 83.8% (CI, 79.0% to 87.8%). Patient loss to follow-up was the major cause of non-SVR. SVR outcomes were equivocal in those with cirrhosis and those without. (129)

A caveat to primary care management of HCV is that cirrhotic patients achieving SVR will still need ongoing monitoring for HCC and regular follow-up, a pathway of care that is best suited to secondary care setting where imaging and Fibroscan® are available on site. However, for non-complex HCV patients it has been postulated that GPs could offer curative therapy in a community setting, and indeed use of this resource will be essential in achieving elimination of the virus (124).

Although there is limited data suggesting HCV RNA positive patients can be managed by GPs there remains an absence of evidence that migrant populations with chronic viral hepatitis can be

managed in primary care settings, and no RCT evidence comparing this with the current standard of care in hospital services.

1.20 Patient Perceptions of Viral Hepatitis, Screening and Treatment

An important consideration in developing a new screening intervention is understanding the attitudes and knowledge of the at-risk population about the disease process, which may be crucial contributors to uptake.

There is limited knowledge and understanding about HBV and HCV in high-risk communities, especially regarding modes of transmission, the asymptomatic nature of chronic infection, and the potential for infection to increase the risk of hepatocellular carcinoma, mortality and morbidity. (130–132) There may also be ongoing stigmatisation around liver disease amongst the immigrant population because of perceived associations with alcoholism and commercial sex workers. (133)

These illness perceptions, combined with other barriers to screening such as language, may contribute to an individual decision as to whether or not to accept a screening test for viral hepatitis infection. However, little is known about the relative contribution of these various factors to screening uptakes.

Prior to the commencement of the HepFREE trial, the study team presented a systematic review aimed at collating evidence on knowledge (illness perception or explanatory models) on HBV and HCV infections among first and second-generation migrants from high or intermediate prevalence countries to low prevalence countries.

Illness perceptions are organised cognitive representations or beliefs patients have about illness, which more inform their behaviours and determine outcomes such as treatment adherence. (134) The explanatory model (EM) of illness has been defined as "notions about an episode of sickness and its treatment that are employed by all those engaged in the clinical process". (135) EMs allow exploration of how illness perceptions are informed by the patient's social and cultural backgrounds. There are several EM models, with common components including aetiology, symptoms, pathophysiology, history and severity (course), and treatment. The Barts Explanatory Model Inventory (BEMI) was compiled through the analysis of studies looking at patients' experience of mental health problems and can be used as either interview (BEMI-I) or questionnaire format (BEMI-C). The latter alone distinguishes amongst explanatory models of ethnic groups and therefore is useful in assessing illness perceptions of large populations from varied backgrounds. (136,137)

The HepFREE team of Owiti et al reviewed 261 studies, of which 51 were found to meet the eligibility criteria of being full text studies focussed on the knowledge of migrants who have moved from

high/intermediate to low prevalence countries. Data was extracted on the knowledge of HBV and HCV infections (including screening, vaccination and treatment) organised around the following themes: concepts of HBV and HCV infection, signs and symptoms, causes, transmission, prevention, consequences and treatment. (131)

Most studies were based in the US (64%) and focussed on the views and experiences of South East Asian immigrants from China, Korea, Cambodia and Vietnam who had moved to the USA, Canada or Australia. Most surveys used a convenience sample (i.e. canvassing the views of attendees at health clinics or community events). There were diverse data collection methods which included focus groups, semi-structured interviews, observational and in-depth interviews and ethnography. Therefore, comparing data across the studies and the various ethnic groups was limited.

1.20.1 Viral Hepatitis Perceptions

Concepts of viral hepatitis for South East Asians included "liver sickness/cancer/disease" and "bad/contaminated/unclean blood" and "yellow skin". Two survey and three qualitative studies noted participants' confusion about the types of viral hepatitis and their progression (for example some participants believed that Hepatitis A/B/C referred to the stages of linear progression through severity of liver disease). Causes of HBV/HCV were attributed to multiple factors such as a "weak liver" (caused by triggers such as smoking, alcohol, stress, hormones). Transmission routes were stated to be contact with contaminated blood/other body fluids (61-90% of participants), pre-masticated food (63-82%), contaminated drug injecting equipment (59-86%) and sharing of toothbrushes and razors (33-86%). Knowledge of vertical transmission ranged widely across the studies with 34-91% of participants being aware of mother-to-child transmission.

Between 54-96% of participant were aware of the HBV vaccine, although there has been evidence that uptake in the Asian-American population has been low (138–145).

1.20.2 Screening Perceptions

Some immigrants expressed general motivation to seek screening (138,145–150). Amongst Cambodian, Chinese and Vietnamese participants screening caused anxiety due to lack of information from HCPs prior to screening (149). Better knowledge of screening processes and understanding of the result outcomes may positively influence engagement. (138,146,149,151,152).

1.20.3 Treatment Perceptions

In nine surveys, 44-96% of participants were aware of treatments for HBV. One study reported knowledge of a lack of effective treatment for HCV. (153) Personal experiences with HBV infection (138,139,148,149,154), having a family member with HBV or liver cancer (31,145,154–156), screening (20,145,157–162), and vaccination (158,162) were associated with better knowledge; though in one study, individuals who had a personal or family history of HBV or liver cancer were more likely to have been screened, but they did not have better knowledge of HBV (145).

This review of the evidence on illness perception and explanatory models showed that the bulk of the evidence emerged from studies on South East Asians in the USA and Canada, and to a lesser extent Australia. There was little evidence of attitudes and understanding amongst migrants from other ethnicities or territories such as South Asia, Africa, Middle East and Eastern Europe and no evidence from those who migrated to the UK. Most of the studies were focussed on knowledge and understanding of HBV infection. One limitation was that the majority of the studies were surveys, with few qualitative studies.

The overall picture was that many (though not all) migrants lack adequate knowledge of the aetiology, symptoms, transmission risk factors, prevention strategies, consequences and treatment of HBV and HCV infections. There was a confusion about various hepatitis types, disconnect in awareness of viral hepatitis and its health implications (especially liver cancer) and poor knowledge of transmission risks, with false attribution to cultural and social factors as well as foodstuffs.

There remains an opportunity to explore the knowledge and understanding in other ethnic migrant groups in the UK, and develop intervention and strategies which could increase uptake in screening programmes for these populations. (131)

1.21 Healthcare Provider Perceptions of Screening and Treatment of Viral Hepatitis

The healthcare provider is a key facilitator to any new health intervention, and general practitioners and other primary healthcare staff can provide a valuable insight into the implementation of a viral hepatitis testing programme and provision of follow-up care in the community. There have been a small number of qualitative studies investigating the primary care providers' perception of HCV case-finding and management.

Qualitative researchers completed semi-structured interviews with 12 PCPs and 12 hepatology providers in Pittsburgh, USA regarding the facilitators and barriers to HCV treatment and adherence. Key barriers were identified as being patients' substance use disorders, mental health, transportation availability, history of non-adherence, and concern about side effects, with PCPs identifying treatment cost as a system-based barrier. The main facilitators were provider education and encouragement, with PCPs also noting patient-based facilitators including past adherence, media exposure to information about HCV medications, a desire to clear the virus, and positive feedback regarding treatment response. (163)

A US study sought the opinions of PCPs on provision of HCV screening as part of the "baby boomer" screening programme offering a one-off test for all those born between 1945-1965. 22 PCPs in six states participated in qualitative semi-structured interviews. Three themes related to primary care provider HCV testing and linkage were identified: (i) evaluating cues to HCV testing (innovation/evidence), (ii) framing HCV testing decisions (recipients), and (iii) HCV testing and linkage to care in the new treatment era (context). The most frequently reported HCV testing cue was an electronic clinical reminder alert, followed by clinical markers and the presence of behavioural risk factors. PCPs indicated a high motivation to test and link patients to specialist therapy. (164)

In New Zealand, one nurse-led practice providing integrated care participated in a qualitative investigation of staff experiences. 24 stakeholders (including 4 clinic staff members and other service providers) were interviewed in depth regarding implementation if the service and interprofessional relationships within the clinic. Participants generally endorsed the clinic model which was thought to support more effective use of health resources. Some participants expressed concerns regarding the potential 'poaching' of patients from other services (particularly general practice) and indicated a preference for HCV treatment services to be restricted to hospital settings. (165)

A large postal survey of 3817 general practitioners in New Zealand assessed perceived barriers to HCV treatment in primary care. 925 (24.2%) surveys were returned. 187 (21%) GPs stated they currently prescribe Hepatitis C medications. 620 (70%) indicated that no general practitioner in their practice had interest in managing Hepatitis C therapy. Hepatitis C training was associated with increased prescribing activity-29% in those with training versus 10% in those without training. Barriers to treatment were identified as inadequate reimbursement (44%), too few Hepatitis C patients (40%), and caseload with other patients (40%), Other barriers included difficulty in

obtaining transient elastography (35%) prior to treatment, lack of training (32%), and the perception that Hepatitis C therapy should be done by a specialist (30%). Also, general practitioners consistently underestimated the prevalence of Hepatitis C in their practice by a factor of 4.3 to 13.6 (based on an estimated prevalence of 1.9%). (166)

All of these studies were focussed on HCV testing and treatment in primary care in either the US or New Zealand. There remains a knowledge gap on the opinions of PCPs in the UK on management of HBV or HCV and whether they believe the migrant population would benefit from the opportunity to access ongoing care in the community.

1.22 Aims and Objectives of the Research

The HepFREE trial was designed to explore the feasibility of testing migrant populations for viral hepatitis in primary care. As Clinical Research Fellow and Trial Manger I collected data and set up community based follow-up clinics for East and South London GP Practices in the trial.

By analysing the HepFREE testing data I aimed to explore the following:

1. To determine the screening rate at practices where GPs are supported and incentivised to screen migrants for viral hepatitis, compared to standard screening rates

and through my own substudy analysis

2. To determine the range of disease staging of those testing positive for viral hepatitis in primary care
3. To determine if community-based follow-up and management is superior to standard hospital based follow-up
4. To analyse the outcomes of the pre-trial survey of eligible patients on their understanding and knowledge of viral hepatitis, and if this influenced their attendance for screening
5. to explore the views and opinions of healthcare professionals on their experience in delivering the HepFREE trial.

In the following chapters I will outline the methodology of the HepFREE trial and each of the substudies, present the data and discuss my research findings, and consider how the findings explain barriers and facilitators to identifying and treating chronic viral hepatitis in immigrants in primary care.

2. Materials and Methods

2.1 The HepFREE Trial

The HepFREE Trial (2013-17) was developed in order to assess the value of screening immigrants for viral hepatitis in a primary care setting, to clarify the prevalence of viral hepatitis amongst this group and to evaluate clinical and cost effectiveness of such a screening programme.

The study involved a preliminary phase of qualitative work examining attitudes to testing and illness perception in several immigrant communities, followed by a randomised controlled cross-sectional cluster trial 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 2%. The trial was developed by Professor Graham Foster and funded by the National Institute for Health and Research (NIHR) through the Programme Grants for Applied Research.

I worked as the London based Clinical Research Fellow (2015-2017) and also the HepFREE trial manager (2016-2017).

This thesis comprises the outcomes of my original analysis of the HepFREE trial data, the outcomes and my original analysis of a community based substudy which was set up and performed by myself. It also includes my original data collection and analysis of disease staging and engagement outcomes, an original qualitative research substudy to the trial which I designed and performed, and my original analysis of patient illness perceptions studies.

In this chapter I discuss the methodology of the main HepFREE Trial, and the HepFREE sub-studies. These are presented below:

(i) <u>Testing for Viral Hepatitis</u>

1. Overall HepFREE Results
2. Disease Staging
3. Engagement and Outcomes in London Community & Standard Care Clinics

(ii) <u>Factors influencing Screening Uptake</u>

4. Patient Pre-Screening Survey
5. The HepFREE Provider Experience Study

In this chapter I will describe the trial design, aims and objectives of the HepFREE trial, from which I developed my original research into engagement and outcomes in London Community Viral Hepatitis Clinics, qualitative research into facilitators and barriers to testing for viral hepatitis in

Primary Care, and further exploratory analysis of the HepFREE outcomes and pre-trial patient survey.

2.2 HepFREE Trial Methodology

HepFREE was a multicentre, open-label, cluster-randomised controlled clinical trial in UK immigrant subjects examining the hypothesis that incentivising and supporting primary care physicians increased screening rates for viral hepatitis in immigrants in areas of high immigrant density (Bradford, North East London and South London). Nested sub-studies examined whether bespoke invitation letters were beneficial and whether community care increased engagement. A parallel non-randomised substudy of screening in a region of low migrant density (Oxford) was also conducted (known as HepFREE 2).

The HepFREE project was initiated with a literature review and qualitative assessment of attitudes to testing and knowledge of viral hepatitis in a variety of immigrant groups. Following completion of these studies, culturally appropriate awareness and information leaflets were developed and used in the communities where testing was to be introduced.

HepFREE Trial Hypotheses:

The trial protocol described the trial hypotheses as follows:

Hypothesis 1

Targeted interventional screening is superior and more cost-effective than control (opportunistic) screening for the detection of viral hepatitis in first and second generation ethnic minority patients in primary care

Hypothesis 2

Provision of an enhanced patient information invitation letters which include additional information on viral hepatitis increases attendance for testing compared to standard information invitation letter.

Hypothesis 3

Community based therapy and follow-up is superior to conventional delivery of treatment (based on referral to local hospital treatment centres) as measured by engagement with management and adherence to therapy.

The Trials:

(1) HepFREE Screening Trial
(2) HepFREE Follow-Up Trial : Standard vs Community Based Clinical Care Trial
(3) HepFREE 2

1. The HepFREE Screening Trial

The main HepFREE trial tested the impact of screening for viral hepatitis in immigrants in General Practices (GP) in three areas of high density of immigrants in England (Bradford, North-east and South-east London). The trial was designed to invite up to 48,000 eligible participants. Practices were randomised to participate in either the intervention arm or the control arm of the trial.

Practices in the targeted intervention arm were further randomised to either the enhanced invitation arm (invitation letters with additional information viral hepatitis) arm or standard invitation letters arm (trial invitation letters are included in Appendix 4), as well as standard or community based follow-up (see details under "2. Follow-Up Trial" below)

Potential participants were identified from all registered patients on the clinical computer systems within the practice by using pre-existing demographic data stored within individual electronic medical records. Once identified, potential study participants were sent an invitation by post to attend for a screening test. Each GP Practice was asked to recruit trial participants over an 18 consecutive calendar months period.

The HepFREE Screening Trial commenced screening on 31 Oct 2013. To avoid a strain on resources, screening start dates were staggered across the practices, with the initial practices commencing screening in Oct 2014, and final practices commencing screening in August 2015. All intervention and control practices were closed to recruitment by 4 February 2017.

2. Follow-up and treatment in Standard vs Community Based Viral Hepatitis Clinics Trial

examine the compliance with clinical follow up and to determine whether or not community care for viral hepatitis was clinically and financially viable we conducted a second trial of different treatment options – therapy in the hospital setting (standard of care) versus therapy in community based viral hepatitis clinics.

This trial was nested within the first screening trial with practices in the targeted screening arm of the first trial randomised to either community care or standard (hospital-based care) in the event of

a positive diagnosis of hepatitis. From the fifty practices that were randomised to the targeted screening arms of the trial, twenty-one were assigned to standard care follow-up and twenty-nine to community care follow-up.

The HepFREE Follow-Up Trial commenced in mid-2014 after patients testing positive for viral hepatitis were identified in the HepFREE Screening Trial.

3. HepFREE 2

A parallel trial was set up in rural Oxfordshire, an area with low density migrant population. GP practices in Oxfordshire were invited to participate as intervention practices only. GPs were asked to invite eligible patients by letter and opportunistically, and recruitment from each practice was not capped. Practices invited patients over an 18 month period, the first practice opened to recruitment in May 2015, and the final practice opened in August 2015.

Patients testing positive for viral hepatitis were referred to secondary care for their ongoing management, but were not followed up by the HepFREE trial.

Data outcomes from HepFREE 2 are included with screening outcomes from the HepFREE trial but are not analysed by me as this work lies outside the scope of this thesis.

2.2.1 Aims and objectives of the HepFREE TRIAL

Aims:

The main aims of the HepFREE trial were:-

1) To complete a literature review of knowledge and attitudes to viral hepatitis in immigrant communities in England

2) To complete a mixed methods assessment of community needs to inform the development of appropriate tools to increase awareness of, and compliance with, testing for chronic viral hepatitis in immigrant communities at high risk of infection

3) To develop a culturally sensitive patient information letter with the potential to increase engagement in testing and treatment

4) To assess the most cost effective method of screening for chronic viral hepatitis in primary care patients within 'at risk' ethnic minority communities.

5) To assess the impact of the interventional approach based strategy to screening.

6) 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.
7) To assess differences in treatment adherence between patients groups receiving treatment within the community against those who have standard hospital care.

Aims 1-3 were addressed with qualitative studies which have been published (131,132)and aims 4 to 7 were addressed in a cluster randomised trial (see below).

For Chapters 3-5 of this thesis, I have analysed data arising from aims 4-7.

Objectives and Outcomes:

The primary and secondary objectives and outcomes from the cluster randomised controlled trial were:-

Primary Objectives

HepFREE Screening Trial

- 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 the screening rate of intervention practices compared to the screening rate in control GP practices

HepFREE Standard vs Community Based Clinical Care Trial

- 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
- To determine the number of eligible patients across the participating GP practices
- To determine the overall level of compliance with diagnostic and prognostic events for all patients that test viral hepatitis positive as part of this trial
- To determine the level of compliance with the management plan for patients that test positive for viral hepatitis.

The Primary and Secondary Outcomes of the HepFREE trial were:

Primary outcomes

- In control GP practices, the number 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). In intervention GP practices: the number of patients eligible for this study that are invited to screen (determined by a review of the number of invitation letters sent to eligible immigrants registered at the GP practice at the initiation of the study).
- The proportion of potential participants that attended for testing
- The proportion of viral hepatitis positive participants that comply with the clinical diagnostic and prognostic assessments in the different treatment arms. Engagement is defined as:
    - completion of three diagnostic and prognostic events (including diagnostic assessment visit, a Fibroscan® and/or ultrasound and a statement of clinical management plan from the hepatology team). The schedule of these events was dictated by local policy.
    - 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.
- The costs associated with delivering the intervention were recorded and used for the cost effectiveness analysis.

Secondary outcomes

- Proportion of new registrants who agreed to undergo testing for viral hepatitis.
- The proportion of patients compliant with their prescribed clinical management plan in the different treatment arms (community care vs standard hospital care). Compliance with the clinical management plan is defined as attending at least one visit after the management plan has been agreed by the participant and the clinicians
- Patients that test positive for viral hepatitis and were prescribed medication to treat their viral hepatitis were monitored for their adherence to therapy. Patients were considered to

have adhered to therapy if they successfully complete 80% or more of their prescribed therapy.

- The 'outcome of therapy' was also monitored. A successful outcome of therapy was defined as sustained viral response 12 weeks after treatment completion for hepatitis C patients. The definition of successful outcome of therapy for hepatitis B treatment is a reduction in viral load to <80% of starting value within 12 weeks.

2.2.2 HepFREE Trial Team

The HepFREE trial team were as follows:
Chief Investigator (CI) – Prof Graham R. Foster
Trial Manager
Data Manager
Clinical Research Fellow (London)
Clinical Research Fellow (Bradford)
Research Assistant (London)
Research Assistant (Bradford)
Research Assistant (Oxford)
Data Manager

The Trial team were all based in London, apart from the Clinical Research Fellow (CRF) and Research Assistant based in Bradford.
I joined the HepFREE Trial team in August 2015 as Clinical Research Fellow (London) and took on the additional role of Trial Manager from Sept 2016 until August 2017.
When I joined the trial, the GP practices in Bradford had been initiated for recruitment (i.e. trained for this research trial and eligible patients identified) by the local CRF. Some practices had started screening in London; however I initiated the majority of GP practices in East London and South London. I also performed a monthly review of testing outcomes at each London practice with the assistance of the Trial Manager and Research Assistant (London).
For the community based clinical care trial I set up new Hepatology clinics at the Royal London Hospital (RLH) and King's College Hospital (KCH) London, and liaised with GP practices to set up new community based Hepatology clinics at 3 practices in East London and 4 in South London.

When I became Trial Manager I also oversaw the collection and cleaning of screening data from interventional and control practices in London, and also the HepFREE2 trial in Oxford. I collected all the research data from the standard and community clinics. At the end of recruitment, I cleaned all the research data with a data manager and assisted in data analysis with the trial statisticians. At the end of the analysis, I wrote the NIHR trial report with Prof G. R. Foster.

2.2.3 Trial Funding, Ethics and Governance

HepFREE was funded by the NIHR through the Programme Grants for Applied Research, after a grant application by CI Prof Foster.

The first version of the Trial protocol was written by the CI and Trial Manager in 2012 and underwent several modifications during the Trial set-up.

The study was sponsored by 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.

The study protocol was approved by the National Research Ethics Service Committee London – Fulham based at HRA NRES Centre Manchester, Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ on 24 December 2012, REC reference number 12/LO/1768.

During 2013 the data for qualitative studies looking at patient illness perception and healthcare providers' experience was collected by qualitative researchers.

During 2013 the HepFREE Trial team was assembled and local co-ordinating leads in Bradford, North East & South East London and Oxford were identified. A Trial Steering committee including of the CI, trial manager, lead statistician, lead qualitative researcher, research fellows and primary care and public health leads was also put together. The trial steering committee was chaired by Prof William Irving (Chairman), supported by Dr Moira Kelly and Dr Alan Montgomery.

2.2.4 Amendments to the HepFREE Protocol

Several modifications were made to the HepFREE protocol during set-up and prior to the commencement of screening. These included the inclusion of the pre-screening survey, and

inclusion of the enhanced letter nested study. However some amendments were made after recruitment had begun (such as the addition of cost-effectiveness analysis), the most significant of which was capping of eligible participants at some interventional GP practices.

2.2.5 Capping of Eligible patients

Several modifications were made to the HepFREE protocol during set-up and prior to the commencement of screening. It was initially planned to test all eligible patients in each practice, on basis that this would be an estimated 500 patients per practice based on prior pilot studies. However between proposal and trial initiation it became clear from eligibility reports that practice mergers had created much larger patient registries, with more than 500 eligible patients at each practice. Between proposal and trial initiation, changes in general practice, specifically the merger of practices to form larger practices with greatly increased numbers of patients, led to a marked increase in the number of patients per practice. A scoping exercise indicated that recruiting from the 58 primary care practices would have led to enrolment of over 100,000 patients –i.e. a doubling of the trial size. As HepFREE is a cluster randomised trial it was not advisable to substantially reduce the number of participating practices. Following discussions with the trial steering committee and funders it was agreed that some practices (35 of the 50) should be 'capped' and recruitment should only involve a total of 500 patients. To determine whether recruitment of all patients from a practice was feasible, the 15 practices that had already initiated recruitment prior to the amendment continued to recruit all eligible patients.

For all 50 practices randomised to the interventional arm, the Clinical Effectiveness Group (London) and Commissioning Support Unit (Bradford) created a search that would enable practice staff to query the GP database (EMIS or SystmOne) to assess the total number of patients fitting the eligibility criteria at the practice. For uncapped practices this list was used to invite all the patients who were flagged as being eligible. For capped practices, a functionality on the GP practice database was exploited to select 500 patients at random who were on the full eligibility list. In capped practices, GP practices invited the 500 patients that were randomly selected by the GP database, and these patients were the eligible cohort at that practice.

For practices where no cap was applied, all identified patients formed the eligible cohort. Patients who were not on the eligible list but who were tested as part of routine care were excluded.

At the end of the intervention period, in control and uncapped practices, the eligibility search was repeated and eligible patients who joined the practice during the study (i.e. present on final but not initial eligibility lists) were included as new registrants. Data was not collected for the number of patients who registered and subsequently left the practice within the 18-month study period.

This amendment was approved in Aug 2014 as part of Protocol version 6.0.

2.2.6 Randomisation of GP Practices

Trial randomisation was performed using the method of online minimisation. The programme managing allocations was web-based, and developed using Java at the Pragmatic Clinical Trials Unit (PCTU), Queen Mary University of London (QMUL) in London, UK.

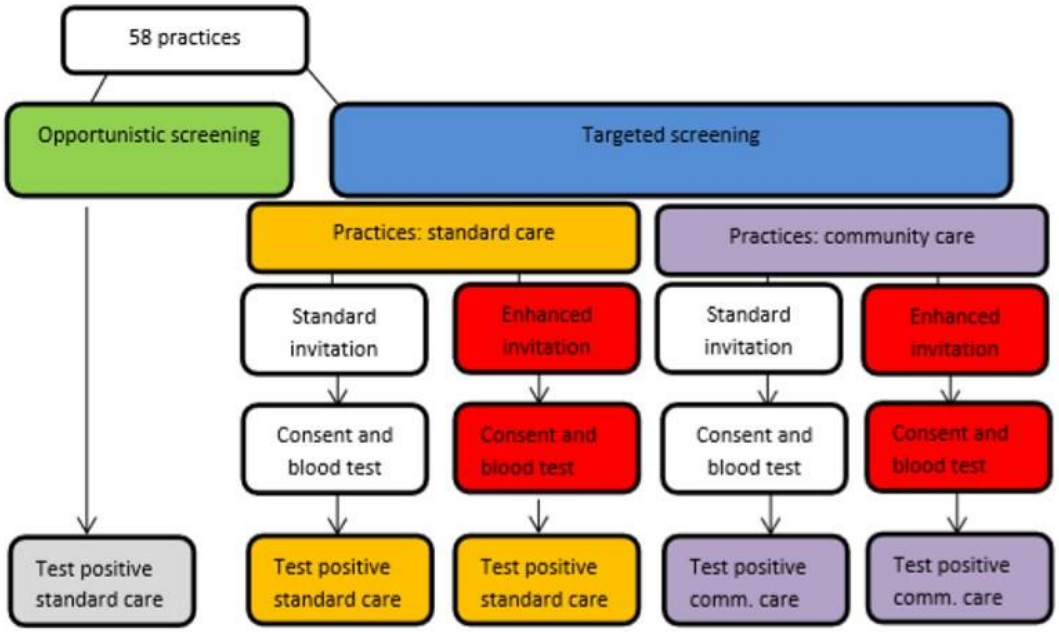
Practices in areas with a high density of migrants were randomly assigned by a trial statistician in the ratio 1:2:2:2:2 to an opportunistic screening (control) group or to one of four targeted screening (interventional) groups: standard (i.e., hospital-based) care and a standard invitation letter; standard care and an enhanced invitation letter; community care and a standard invitation letter; or community care and an enhanced invitation letter.

There were therefore five treatment groups, which were first stratified by area (Bradford, southeast London, or northeast London) and then minimised by number of eligible patients per practice. This method was used in preference to minimisation with a random element, which has limitations when it is required to allocate different numbers of clusters to different trial groups, as in this case.

Practices were divided into three groups according to the number of eligible patients: fewer than 1600 patients, 1600–3300 patients, or more than 3300 patients. Randomisation was done with an online minimisation system that was developed by, and hosted at, the PCTU, QMUL. This cluster randomisation study design minimised training and spillover effects. Clusters consisted of all migrants registered at a practice (or a random subset of such patients) and interventions were delivered at the cluster level in parallel interventions. Patients registered with the practice were not informed of their allocation, but the practices were aware.
The trial manager emailed the details of which GP practices needed to be randomised directly to an independent PCTU statistician (who had no other involvement in the trial), who used the randomisation software to allocate the practice, and the project coordinator was then notified by

email of the allocation group. The analysis team were masked to the allocation groups. Patients who tested positive for viral hepatitis were not informed of the group to which their practice was allocated until after they consented to enter the embedded trial of community versus standard care.

Figure 5: HepFREE Trial design



2.2.7 Consent

The HepFREE Screening Trial was a cluster randomised trial of screening. Therefore, there was no individual participant consent to participation. Participants gave written consent to the blood test used for screening and for access to data. At this stage they were blinded to their practice's treatment allocation in the second trial so were unaware of their treatment in the event of a positive screening result.

Consent to participate in the HepFREE Follow-Up Trial was sought from all participants who had a positive viral hepatitis screening test at the time of their diagnostic assessment in secondary care. Once this consent to the second trial had been obtained, participants were un-blinded and informed of their practice's 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 who withdrew consent for the second trial was treated as per standard care. Treatment allocation was concealed until after the initial consent to participate in the second trial had been obtained, in an effort to prevent bias from being created between recruitment in the two arms of the trial.

2.2.8 HepFREE Screening Trial Methodology

2.2.8.1 The control arm

Practices randomised to the control arm received detailed written information about the trial aims, objectives and methods and a single face-to-face meeting with the trial team at a site initiation visit (SIV). The SIV was attended by general practitioners (GPs), the practice manager, practice nurse and healthcare assistants and consisted of an education session on viral hepatitis delivered by the local Clinical Research Fellow with the use of PowerPoint presentation. Information included indications for screening and consequences of long-term infection.

The purpose of the session was to encourage practitioners to offer screening to individuals considered at risk of viral hepatitis, including individuals who would have been eligible if the practice had been randomised to targeted screening. Clinicians were encouraged to consider offering the screening test to eligible individuals who attended the practice for a consultation or when registering as a new patient.

A copy of the slides and documents provided in the SIV is found the in Appendix 3.

2.2.8.2 The targeted screening (intervention) arm

Practices in the intervention arm were allocated to be given a financial incentive for every patient tested, and patients received either a standard or enhanced invitation letter. Practices were visited by the trial team at an SIV where members of staff received the same education session provided to control practices, as well as teaching on additional trial procedures. In practices assigned to targeted screening, potential study participants were invited to attend for screening using one of the two trial invitation letters (see appendix 4).

Administrative staff were taught how to generate and distribute personalised screening invitation letters using the practice computer system. 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 participant's electronic medical record and instructions were given on how to refer a participant to the HepFREE trial team in the event of a positive screening test result.

2.2.8.3 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. In practices performing targeted screening financial support was provided by NIHR. Table 1 summarises the payments made to targeted screening practices for trial related activities.

Table 4: Study support costs provided to targeted screening practices 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

2.2.8.4 Eligibility 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 at the in appendix 2).
- 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 patients immunised for HBV.

Patients could withdraw from the trial at any time and data up to the time of withdrawal was retained and analysed.

2.2.8.5 Patient selection

In London and Bradford each practice manager ran a bespoke eligibility search report on their GP database (the SystmOne database for Bradford practices and some London practices and the EMIS database for all other London practices). The reports were designed in conjunction with the data quality team at the Yorkshire and Humber Commissioning Support Unit (CSU and the Clinical Effectiveness Group (CEG) at the Centre for Primary Care and Public Health, QMUL.

For GP databases using SystmOne (S1), the eligibility search consisted of two reports that were combined and when run at the same time on S1 created 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 'eligible' individuals, 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 produced a final report containing the details of all individuals that fulfilled the criteria for enrolment. This list was used by practice administrative staff to generate and distribute letters. Practices recruited to 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.

At practices using EMIS a single eligibility search was run at the start of the study and identified eligible patients based on

- Country of birth
- Main spoken language
- Ethnicity

Patients were excluded who had either already been diagnosed with chronic viral hepatitis or had undergone testing for viral hepatitis in the previous five years. In practices assigned to test all

patients a second report (Final Eligibility) was run at the end of screening and identified patients on the same basis as the initial report and therefore included new patients who had registered at the practice during the 18 months study period and were eligible for screening. At the end of the screening period a final screening report was run at each practice to capture date invitation letter sent, patient consent to trial recruitment, date of HBsAg and anti-HCV testing, and outcome of testing. For practices recruited to perform selective, capped enrolment, the 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 either SystmOne or EMIS 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 SystmOne or EMIS 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.

At control practices using EMIS a screening report was run at the end of the 18 month period to identify date of HBsAg and/or anti-HCV testing and outcomes.

In summary the reports were:

SystmOne Practices:

(i) Report 1 – identifying eligible patients
(ii) Report 2 – excluding previously screened/known positive patients from Report 1.
(iii) Combined report – combining outcomes from Reports 1 & 2
(iv) Random 500 Report – selecting 500 randomised patients from (iii)
(v) Screening Report (based on either (iii) or (iv)

EMIS Practices:

(i) Initial Eligibility report – those patients eligible for screening on Day 1 of the 18 month screening period
(ii) Final Eligibility Report – those patients eligible for screening on final day of 18 months screening period
(iii) Random 500 report – selecting 500 randomised patients from (i)
(iv) Screening report – based on (ii) or (iii)

Control Practices

(i) Initial Eligibility report – those patients eligible for screening on Day 1 of the 18 month screening period

(ii) Final Eligibility Report – those patients eligible for screening on final day of 18 months screening period

(iii) Screening report – based on (ii)

It was accepted that there may have been a small number of eligible patients who joined and left practices within the eighteen months of the screening period and therefore would not appear on either (i) or (ii) at Uncapped or Control practices.

For patients identified as eligible for the study an invitation letter was sent inviting attendance and participation in the trial. In addition the patient's electronic letter was 'flagged' to identify them as eligible for testing and when such patients attended the surgery they were asked if they wished to participate.

2.2.8.6 Data capture during the screening

A trial-specific template that incorporated and collected data required for analysis was designed by CEG and was built and published on SystmOne (Bradford) and EMIS web (London) for data capture. 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 (with attached Read code) or free text entry.

- The date the person either agreed or declined the offer to give blood for testing
- The date consent to give blood for testing 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 consent.

There were two fields on the template to record a positive HBV or HCV screening test result and either this could be used or the Read codes could be entered manually without opening the template. Monthly cumulative reports 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

screening and the results of all screening tests were sent to London by secure email for cleaning by the trial study team and storage by the trial data manager.

2.2.8.7 Testing of patients in the HepFREE Trial

Patients were identified as eligible for HepFREE screening using the bespoke trial eligibility search and invited by letter to participate in the trial at their GP practice. Additionally, an electronic alert was placed on the patients' electronic records system (either EMIS or SystmOne) identifying them as eligible for testing, so that patients could be opportunistically asked to participate if they attended the GP practice for another reason.

Patients who responded to invitation were asked for written consent to take blood and use the results in the trial. Following consent, 6 millilitres of venous blood was obtained by venepuncture and sent in a 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 (Leeds General Infirmary for Bradford, Barts Health Virology for NE London and Kings College Hospital virology for SE London).

HepFREE study samples were tested and reported as follows:

<u>HBsAg</u>

Blood samples were tested using the Abbott ARCHITECT HBsAg qualitative assay. This is a two-step chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of hepatitis B surface antigen (HBsAg) in human serum and plasma.

Samples that tested positive 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.

Samples that tested HBsAg negative were reported to the referring GP. No further action was required.

<u>Anti-HCV</u>

Samples were tested for anti-HCV using the Abbott ARCHITECT Anti-HCV assay (Abbott Laboratories. Abbott Park, Illinois, U.S.A.). ARCHITECT Anti-HCV assay is a CMIA for the qualitative detection of

immunoglobulin G (IgG) and immunoglobulin M (1gM) antibodies to hepatitis C virus (anti-HCV) in human adult serum and plasma.

Anti-HCV Positive

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. 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.

The sample was also automatically referred for RNA testing 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 RNA in human plasma or serum. The results of this test were reported to the referring GP.

Anti-HCV negative

The screening test for HCV was negative and reported to the referring GP. No further action was required.

Low level anti-HCV

For those samples reported as either low level anti-HCV or anti-HCV indeterminate, 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.

2.2.8.8 Management of patients identified with chronic viral hepatitis and individual consent for participation in the HepFREE follow-up trial

Participants with a positive screening result were contacted by a member of staff in the practice and an appointment made with a practice clinician. As the Clinical Research Fellow, I generated a referral for the participant to attend secondary care and notified the patient by letter to their home address and also by mobile phone text reminder.

Irrespective of the patient's further participation in the Follow-up Trial all diagnostic investigations were scheduled at the patient's local Hepatology Secondary Care Centre to be seen by the Clinical Research Fellow (myself in North-east and South-east London). All subsequent follow-up

appointments in either standard or community care in London were arranged and conducted by myself.

2.2.8.9 Data Capture

Data capture for patients with a positive test result was recorded on the OpenClinica open source clinical trial software for Electronic Data Capture Clinical Data Management. This allowed the recording of case report forms for study events such as:

- Patient Demographics (Ethnicity, Country of Birth, Study location, Date of positive results, anonymised identifiers)
- Diagnostic Assessment (documentation of supplementary consent, blood results including full blood counts, Liver function tests, INR, renal function and HIV viral hepatitis screen)
- Fibrosis Assessment (documentation of liver ultrasound, liver biopsy and Fibroscan® results)
- Management (approved therapy, observation, wait for new therapies or refer to clinical trial for treatment)
- Extra Visits (summary of additional clinic visits in hospital or community setting)
- Adverse Events

Demographics

Patient demographics recorded for all those testing positive for HBsAg and HCV Ab were

- Gender
- Ethnicity
- Country of birth

Some of the above were included in GP records, but full documentation was recorded at the time of the patient's presentation to diagnostic screening appointment in secondary care.

Tests and staging for HBV infection

For patients testing HBV sAg positive, staging investigations were:

- Hepatitis B specific serology tests: Hep B core antibody, Hepatitis B e-antigen, Hepatitis B e-antibody, Hepatitis B DNA levels and Hepatitis delta co-infection
- General serology tests: full blood count, urea and electrolytes, liver function tests, HIV antibody.
- Imaging investigations: liver transient elastography and liver ultrasound.

- Liver Biopsy: Some patients based in the Bradford arm of the study were offered a liver biopsy as per local protocol

Staging for Hepatitis B infection is dependent on HBV viraemia, and imaging.(21)

Tests and staging for HCV infection

HCV Ab positive, HCV RNA negative status reflects patients who have either been treated and cured of HCV, or have self-cleared the virus (approx. 20% of those infected). (36)

For those testing positive for HCV Ab, a negative HCV PCR test confirmed by a repeat negative test confirms a non-viraemic status. These patients can be discharged without follow-up, requiring a HCV RNA test only if they are at further risk.

For patients testing HCV-antibody and HCV RNA positive, staging investigations were:

- Hepatitis C specific serology tests: HCV Genotype, HCV RNA levels.
- General serology tests: full blood count, urea and electrolytes, liver function tests, HIV antibody.
- Imaging investigations: liver transient elastography and liver ultrasound.

NB: Liver Biopsy: - Some patients based in the Bradford arm of the study were offered a liver biopsy as per local protocol at the time of the study. However, this was not a measured outcome for the HepFREE trial.

Staging for Hepatitis C infection is dependent on imaging. (3,36)

HIV Testing

HIV Antibody testing was routinely offered to all patients testing positive for HBV or HCV or both as part of local protocols.

2.2.8.10 Data Collection Process

Trial 1: The following information was collected from participating GP practices at the end of the 18 months screening period:

- Number of eligible patients [patients WITHOUT a positive Hepatitis B and C status on file] at this GP Practice (over total screening period) and their ethnicity and gender breakdown. For capped practices the number of eligible patients was 500 and the number of eligible patients varied in the other practices.

- Total numbers of eligible patients contacted for screening (over the 18 months screening period)
- Total numbers of patients screened at a new patient appointment
- Total numbers of new registrants screened – i.e. patients registering with the practice after the practice was initiated and has not left the practice up until the practice was closed for screening
- Total numbers of patients test positive for viral hepatitis

The data was collected by running bespoke HepFREE eligibility searches which were prepared by the Primary Care Trials Unit, QMUL for use on SystmOne and EMIS systems. The searches were powered to look for patients fitting the above parameters at set timepoints (start and end of screening period). They also allowed collection of anonymised patient demographics.

Patient level data was collected from patients who agreed to be tested. This included:

- Age
- Gender
- Ethnicity
- Country of birth
- Country of parents' birth
- Blood testing results

2.2.8.11 Data Management

Clinical fellows and research assistants were responsible for collecting cumulative monthly reports from each intervention practice for storage and cleaning. At the end of the trial, a final screening report was run at each control and intervention practices. All of these reports included the Read codes and outcomes for the parameters described above in Data Capture section 2.2.8.9. Initial data cleaning was undertaken by a data manager and myself in my role as the clinical research fellow. We ensured that all patients identified as eligible fit criteria of at least one of (i) country of birth, (ii) main language spoken or (iii) ethnicity, in both control and intervention practices. Patients belonging at intervention practices required evidence of eligibility (from the eligibility reports) presence of a consent form or electronic consent code, date of invitation, date of testing and outcome of screening. The patient's practice was contacted for relevant missing data.

For missing test outcomes, the virology laboratory was contacted and a result of negative, positive or sample missing was recorded. Missing data were then manually entered. For patients screened at Control practices, they required evidence of eligibility (from the eligibility reports), date of testing and outcome of screening to be included as a screened participant. Again, if any results fields were missing, the virology laboratory was contacted to clarify outcomes. Final cumulative reports of eligible patients from SystmOne practices, from uncapped EMIS practices and from capped EMIS practices were produced. A final cumulative screening report for SystmOne and for EMIS practices was also produced and cross referenced with the eligibility reports to produce a final outcome of eligible, screened patients from each practice. Patients with positive test results were identified from the monthly screening reports and positive READ codes from the virology laboratories.

Therefore there were two possible routes of identification for positive results which were applied to both control and active practices. Results that were positive at the surgery but negative in the virology laboratory were reviewed and, where appropriate, the GP result was deleted. Results that were positive in the virology laboratory but reported negative at the GP surgery were reviewed and, if appropriate, the GP record was amended and the patient contacted to inform them of the positive result.

2.2.9 HepFREE Trial Data Analyses

The following statistical methodology is from the HepFREE protocol version 9 (see appendix 1) and statistical analysis plan. This analysis was completed by an independent statistician from PCTU, and is included here for completeness.

2.2.9.1 Trial definitions

HepFREE Screening Trial:

Screening rates = standard screening vs interventional screening (8 v 50 practices)

Denominator = the number of individuals deemed eligible to be screened at each GP practice over the 18 months screening period. (In standard and interventional screening practices where all eligible individuals were invited, the number deemed eligible was the number of individuals fulfilling the eligibility criteria over the 18 months screening period and in intervention practices where only 500 individuals were randomly selected for inviting, the denominator was 500).

Numerator = number of patients attending a blood test and for whom the GP practice received their results over the 18 months trial period.

HepFREE Follow-Up Trial:

Engagement with Clinical Assessment rates (binary outcome) in community care vs standard care:

Numerator – number of patients engaged with clinical assessment.

Engagement with diagnostic and prognostic assessment was defined as completion of three diagnostic and prognostic events (including diagnostic assessment visit, a Fibroscan® and/or ultrasound and a statement of clinical management plan from the HepFREE Clinical Research Fellow).

The schedule of these events was dictated by local policy. For patients who were HCV antibody positive but HCV RNA negative, attending the GP practice or the local hospital on two separate occasions was deemed as adherence with diagnostic and prognostic assessments.

Denominator – number of patients tested positive for viral hepatitis. Patients who tested positive, but did not come to receive their results after contacting them on three separate occasions were recorded as “not-engaged”.

Compliance to Clinical Management Plan and Prescribed Therapies: community vs standard care

Compliance with the clinical management plan was defined as attending at least 1 visit within 6 months after the management plan was been agreed by the participant and the clinicians. Patients that tested positive for viral hepatitis and were prescribed medication to treat their viral hepatitis were monitored for their adherence to therapy. Patients were considered to have adhered to therapy if they successfully completed 80% or more of their prescribed therapy.

Secondary Outcomes

HepFREE Screening Trial:

(i) for each ethnic group estimated prevalence rates of viral hepatitis. Calculated as number of patients screening positive in the first trial over number of patients screened

(ii) for each ethnic group positive screening rate of viral hepatitis. Calculated as number of patients screening positive in the first trial over number eligible for screening

(iii) Screening rates in new registrants for viral hepatitis (only applicable for practices offering 'uncapped' interventional screening or standard screening). Numerator = number of new registrants attending a blood test and for whom the GP practice has received their results over the 18 months trial period. Denominator = the number of new registrants deemed eligible to be screened at each GP practice over the 18 months screening period. (A new registrant is any person registering with the practice after the initiation date and has not left the practice up until the date practice was closed for screening).

HepFREE Follow-Up Trial:

(iv) Sustained virological response (SVR): For patients with hepatitis C, SVR is defined as undetectable HCV RNA (i.e. viral load below 18IU/ml) 12 weeks after DAA treatment completion, or 24 weeks after Interferon based treatment. The definition of SVR for hepatitis B treatment is a reduction in viral load by >80% of starting value within 12 weeks. Denominator – number of patients went on to have at-least one dose of anti-viral therapy. Numerator – number of patients deemed successfully treated based on SVR outcomes.

2.2.9.2 Sample size calculations

In our original sample size calculation, we assumed that there are 500 eligible (i.e. high risk because of country of birth/ethnicity) patients per practice, on average. However, as the practice recruitment progressed it was clear that the number of eligible patients in some practices could be 3 to 4 times

(approximately 2000 eligible patients) more than what we had anticipated, and revised our original calculations accordingly.

Original sample size calculation

We powered our study to detect a difference of 25% (from 15% for opportunistic screening to 40% for targeted screening) in testing rate for screening trial, and a difference of 20% in engagement rates (from 50% for usual care to 70% for community care) for the nested treatment trial. For the nested trial we assumed an average of 500 eligible patients per practice, 40% screened and 3% testing positive (5% prevalence for 50% born abroad, 1% prevalence for 50% UK born), hence an average of 6 identified infected patients included in the nested treatment trial per practice. We use an intra-cluster correlation coefficient of 0.05 and a coefficient of variation of cluster size of 0.65. This resulted in 185 patients or 31 clusters being required in each arm for a power of 90% and alpha of 5%. Thus we required 62 practices altogether in the nested trial.

For the screening trial, with 500 eligible patients per practice, an ICC of 0.05 and coefficient of variation of cluster size of 0.65, 2666 individuals or 6 practices are required in each arm. With 62 practices in the targeted screening arm, 6 further practices in the opportunistic testing (control) arm would have given us more than 90% power to detect our specified difference. We increased the number of practices on the control arm of the screening trial to allow for drop-outs.

Revised sample size calculation.

We continued to assume an intra-cluster correlation coefficient of 0.05 for all outcomes, a coefficient of variation of cluster size of 0.65, and that 40% of eligible patients would be screened and of these 3% would test positive. In practices where there were 2000, rather than 500, eligible participants this would result in 24 participants included in the nested treatment trial. To detect a difference from 50% to 70% engaged with 90% power at the 5% significance level requires 134 participants in each arm without allowing for clustering, or 268 altogether. As described in section 8, following the realisation that the number of eligible participants in practices was on average 2000 and not 500, we decided to approach all eligible participants (i.e. on average 2000) from 15 practices, and then re-estimated the number of additional practices needed in the nested treatment trial to reach an effective sample size of 268. We estimated that we would need an additional 31 practices. We increased the number of practices needed to 50 overall to allow for drop outs.

2.2.9.3 Statistical Analyses

All analyses were documented in a detailed analysis plan that was signed off by the senior statistician and chief investigator prior to the release of allocation codes to the statistician. We used statistical analyses for two comparisons in trial 1 (HepFREE screening trial) and three in trial 2 (HepFREE follow-up trial). Other potential comparisons were not undertaken because of small numbers of participants. In trial 1 loss to follow-up and missing data was not relevant. In trial 2 for the analysis of overall engagement with diagnostic and prognostic events withdrawals, patients lost to follow-up were recorded as not engaged. Only those who withdrew consent for use of their data were excluded from the analyses. For the treatment compliance, treatment adherence and viral response in stage 2, patients lost to follow-up or withdraw consent were retained and used in the analysis up to the point of withdrawal. Where feasible, reason for withdrawal were documented and presented in the CONSORT diagram. Patients who died were excluded from analysis. In trial 1, and in the embedded trial of invitation letters, comparisons of screening rates were modelled using Poisson regression models. Our dependent variable was number of patients screened in each GP practice. The number of eligible patients was included as the exposure and practice as a random effect. The stratification factor, area, was included as a covariate in the model. The model was checked for over-dispersion. Intra-cluster correlation coefficients (ICCs) calculated. If ICCs were found to be negative, the intervention effects from the analysis not adjusting for clustering are presented.

In the Follow-up Trial:

1) engagement in community based therapy compared to hospital based therapy 2) engagement with diagnostic and prognostic events in community based therapy compared to hospital based therapy 3) compliance with clinical management plan in community based therapy compared to hospital based therapy

For the engagement outcome, generalised estimating equations using logit link to account for binary outcome, accounting for area, cluster size (number of eligible patients group), age and sex (xtgee command in Stata) were fitted. Model based ICCs are presented. Exchangeable correlation matrix and robust standard errors were used. Where ICCs were negative, the intervention effects from the analysis not adjusting for clustering is presented.

2.3 Disease Staging Outcome Analysis

Patients who tested positive in the intervention of the HepFREE screening trial had also consented to the ongoing collection of data regarding their disease stage and management. This data was

collected on the OpenClinica platform and collated on Microsoft Excel for descriptive and exploratory analysis by me. This included demographics (gender/age/country of birth) and serological results, Transient Elastography score and ultrasound reports.

Statistical analysis was performed on Stata program version 14.

2.4 London Standard Care Community & Clinics Follow-Up Trial

Patients testing positive for viral hepatitis at primary care practices employing interventional screening were cluster randomised into two follow-up arms: standard hospital clinic follow-up, or community based follow-up. In both arms, patients who tested positive were referred to their local hospital for an initial diagnostics appointment. At this visit, the patients were provided with a detailed information sheet explaining the follow-up phase of the trial, and were asked to provide written consent to be for progression to Stage 2 of the Hep FREE study.

2.4.1 London GP practices

In London, as the 32 interventional practices were spread across East London (17 practices) and South London (15 practices), patients testing positive were referred to either Royal London Hospital (North East London) or King's College Hospital (South East London).

Any patient who tested positive in East London was referred for diagnostic and prognostic tests at the Royal London Hospital (RLH), Whitechapel. East London is defined as the boroughs of Tower Hamlets, Newham and Redbridge and their associated Clinical Commissioning Groups (CCGs).

Any patient who tested positive in South London was referred for diagnostic and prognostic tests at King's College Hospital (KCH), Denmark Hill. South London is defined as the boroughs of Lambeth and Southwark and their associated Clinical Commissioning Groups (CCGs). CCGs are responsible for commissioning hospital and community services in their local areas and assured by NHS England.

Tables 5 and 6 list the London GP practices, their boroughs and CCGs, and nominated Community Care centres. Figures 6 and 7 show the geographical distribution of GP practices in East and South London with their associated local Secondary Care Centres and Community Care Centres.

Table 5: East London GP Practices and associated Secondary and Community Care Centres

Area	Clinic Map Number	Practice	Borough	Secondary Care Centre	Community Care Centre
EAST London	1	Stroudley Walk Health Centre E3 3EW	Tower Hamlets	Royal London Hospital E1 1FR	NA
EAST London	2	Royal Docks Medical Practice E6 5NA	Newham	Royal London Hospital E1 1FR	NA
EAST London	3	Dr Driver & Partners (aka Forest Practice) E7 0EP	Newham	Royal London Hospital E1 1FR	NA
EAST London	4	Star Lane Medical Centre E16 4QH	Newham	Royal London Hospital E1 1FR	NA
EAST London	5	Greengate Medical Centre E13 8PS	Newham	Whipps Cross Hospital E11 1NR	NA
EAST London	6	Ilford Lane Surgery IG1 2SN	Redbridge	Whipps Cross Hospital E11 1NR	NA
EAST London	7	Queen Mary Practice E18 2QS	Redbridge	Whipps Cross Hospital E11 1NR	NA
EAST London	8	Jubilee Street Practice E1 0LS	Tower Hamlets	Royal London Hospital E1 1FR	Jubilee Street Practice E1 0LS
EAST London	9	Dr Patel's Surgery E7 8LZ	Newham	Royal London Hospital E1 1FR	Dr Abiola Practice E7 0EP
EAST London	10	Stratford Village Medical Practice E15 4BZ	Newham	Royal London Hospital E1 1FR	Dr Abiola Practice E7 0EP

EAST London	11	Dr Abiola Practice (aka Forest Practice) E7 0EP	Newham	Royal London Hospital E1 1FR	Dr Abiola Practice E7 0EP
EAST London	12	E12 Health Centre E12 6AQ	Newham	Royal London Hospital E1 1FR	Dr Abiola Practice E7 0EP
EAST London	13	Leytonstone Road E15 1LH	Newham	Royal London Hospital E1 1FR	Dr Abiola Practice E7 0EP
EAST London	14	Cumberland Medical Centre E13 8LS	Newham	Royal London Hospital E1 1FR	Dr Abiola Practice E7 0EP
EAST London	15	York Surgery IG1 3AF	Redbridge	Whipps Cross Hospital E1 1FR	Dr Abiola Practice E7 0EP
EAST London	16	St Andrews Health Centre E3 3FF	Tower Hamlets	Royal London Hospital E1 1FR	St Andrews Health Centre E3 3FF
EAST London	17	XX Place Health Centre E1 4DG	Tower Hamlets	Royal London Hospital E1 1FR	St Andrews Health Centre E3 3FF

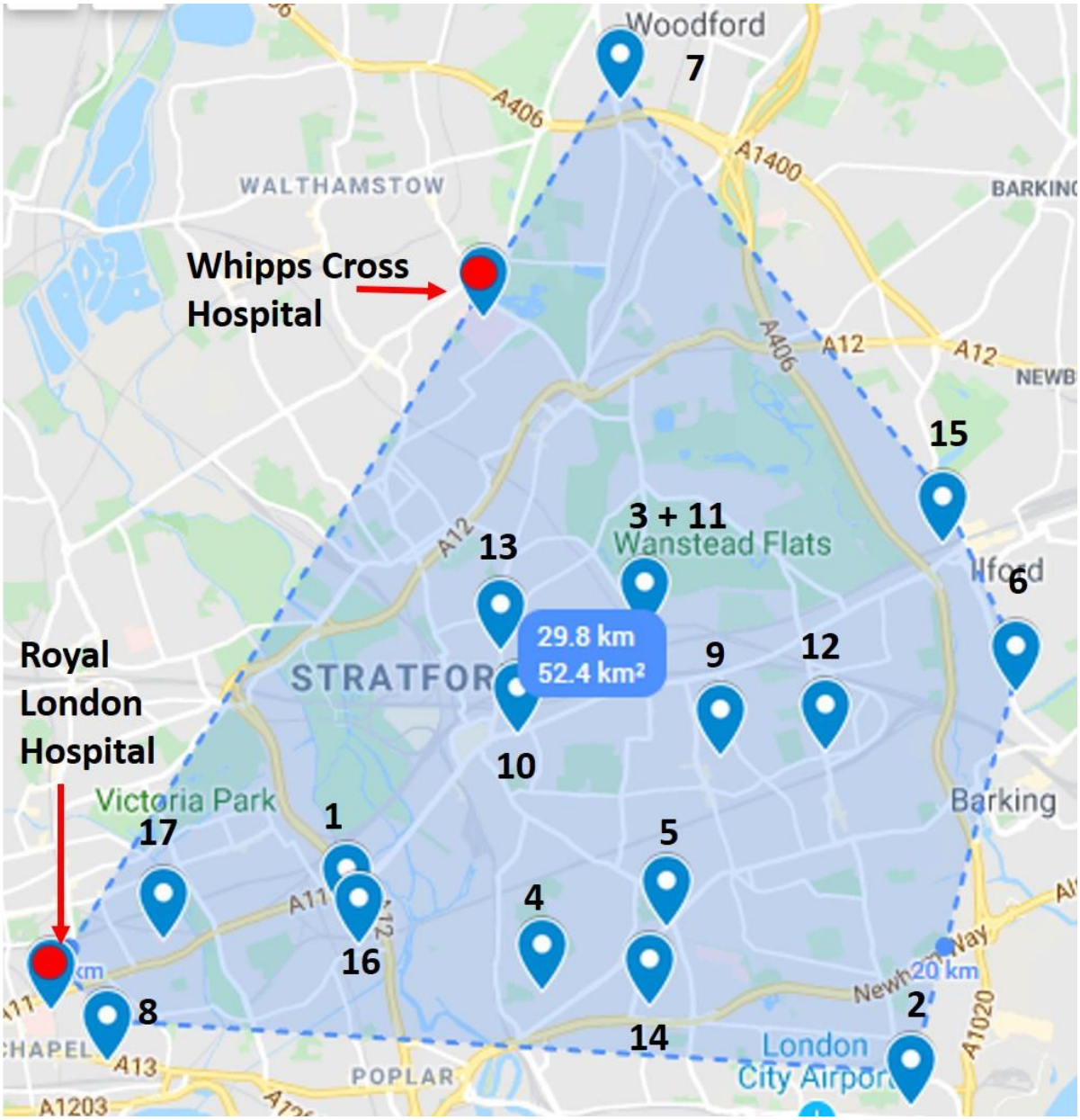


Figure 6: Geographical Distributions of the East London GP Practices

Table 6: South London GP Practices and associated Secondary and Community Care Centres

Area	Clinic Map Number	Practice	Borough	Secondary Care Centre	Community Care Centre
SOUTH London	1	Minet Green SW9 6AF	Lambeth	King's College Hospital SE5 9RS	NA
SOUTH London	2	Riverside Medical Practice SW8 2JB	Lambeth	King's College Hospital SE5 9RS	NA
SOUTH London	3	Streatham Common Practice SW16 5LS	Lambeth	King's College Hospital SE5 9RS	NA
SOUTH London	4	Acorn & Gaumont House Surgeries SE15 5SL	Southwark	King's College Hospital SE5 9RS	NA
SOUTH London	5	Dr Bradford and Partners (aka East Street Surgery) SE17 2SX	Southwark	King's College Hospital SE5 9RS	NA
SOUTH London	6	Paxton Green Group Practice SE21 8AU	Southwark	King's College Hospital SE5 9RS	NA
SOUTH London	7	Hurley Clinic SE11 4HJ	Lambeth	King's College Hospital SE5 9RS	Manor Place Surgery SE17 3BD
SOUTH London	8	Manor Place Surgery SE17 3BD	Southwark	King's College Hospital SE5 9RS	Manor Place Surgery SE17 3BD
SOUTH London	9	Lambeth Walk Group Practice SE11 6SP	Lambeth	King's College Hospital SE5 9RS	Manor Place Surgery SE17 3BD
SOUTH London	10	Hetherington Practice SW4 7NU	Lambeth	King's College Hospital SE5 9RS	Sir John Kirk Close Surgery SE5 0BB

SOUTH London	11	The Iveagh Surgery SW9 6AF	Lambeth	King's College Hospital SE5 9RS	Sir John Kirk Close Surgery SE5 0BB
SOUTH London	12	Herne Hill Road Medical Practice SE24 0AU	Lambeth	King's College Hospital SE5 9RS	Sir John Kirk Close Surgery SE5 0BB
SOUTH London	13	Sir John Kirk Close Surgery SE5 0BB	Southwark	King's College Hospital SE5 9RS	Sir John Kirk Close Surgery SE5 0BB
SOUTH London	14	Albion Street Practice SE16 7JX	Southwark	King's College Hospital SE5 9RS	Albion Street Practice SE16 7JX
SOUTH London	15	Crown Dale Practice SE19 3NY	Lambeth	King's College Hospital SE5 9RS	Crown Dale Practice SE19 3NY

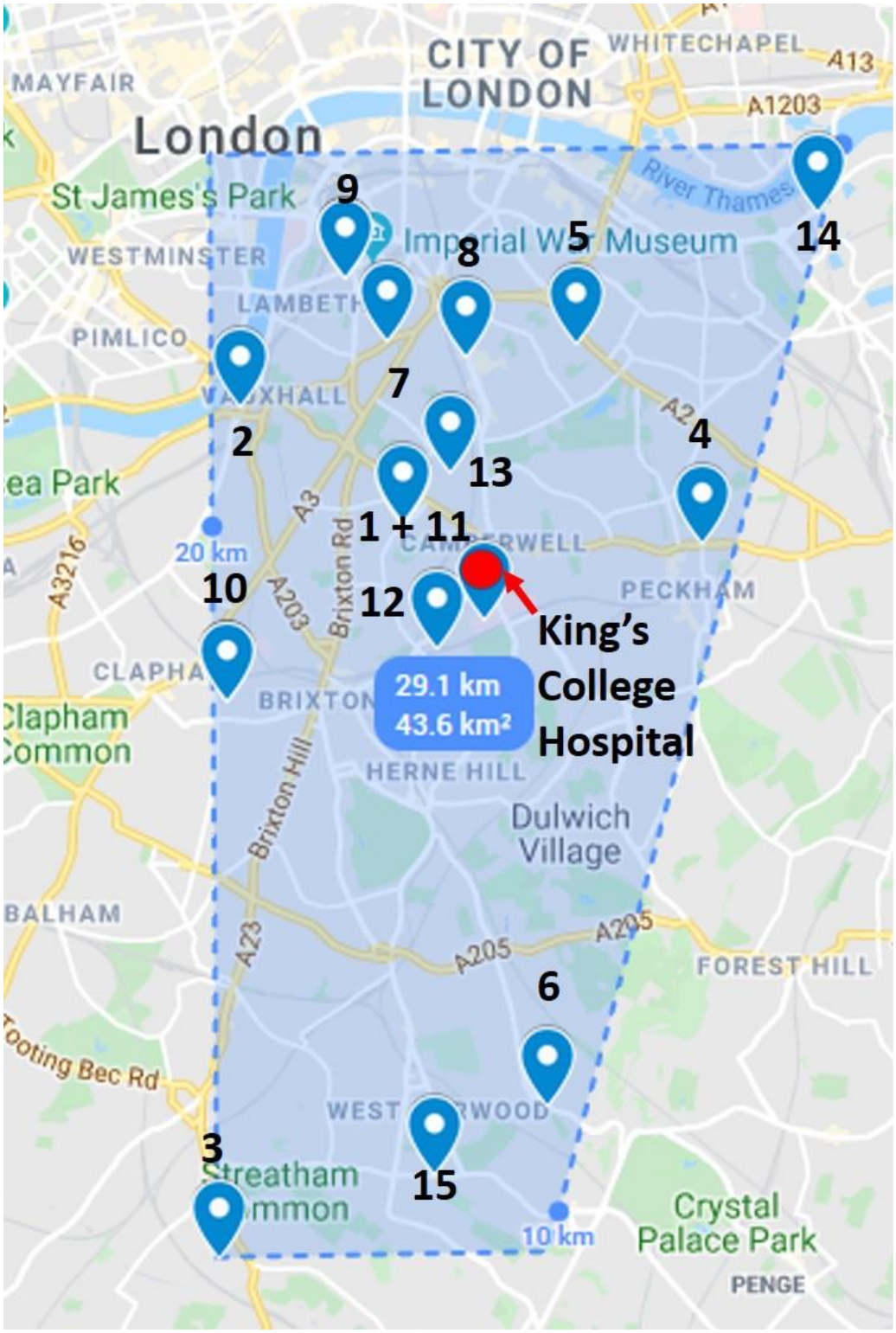


Figure 7 Geographical Distributions of the South London GP Practices

2.4.1.1 Distribution of Community Care Centres

Due to the wide geographical spread of practices, 3 practices were used for community care in East London and 4 in South London. Several factors dictated which practices would be suitable as community care centres:

(i) The practice must be a cluster randomised to a community care follow-up

(ii) The practice lead GP must be agreeable to the practice being used as a community care location

(iii) The practice should be geographically nearer to the patient's original practice than the local secondary care centre

The East London community practices were:

- Dr Abiola Practice, Lord Lister Health Centre, 121 Woodgrange Road, London E7 0EP
- Jubilee Street Practice, 367-374 Commercial Road, London E1 0LS
- St Andrews Health Centre, 2 Hannaford Walk Bow, London E3 3FF

The South London community practices were:

- Albion Street Group Practice, 87 Albion St, London SE16 7JX
- Manor Place Surgery, 1 Manor Place, London, SE17 3BD
- Sir John Kirk Close Surgery, 3 Sir John Kirk Close, London, SE5 0BB
- Crown Dale Medical Centre, 61 Crown Dale, London, SE19 3NY

As above, Tables 1 & 2 show the GP practices and their linked community centres. Figures 5-8 show the geographical distribution of the GP community centres and the locally linked practices. Jubilee Street practice (in East London) is not shown as it had no other locally linked practices.

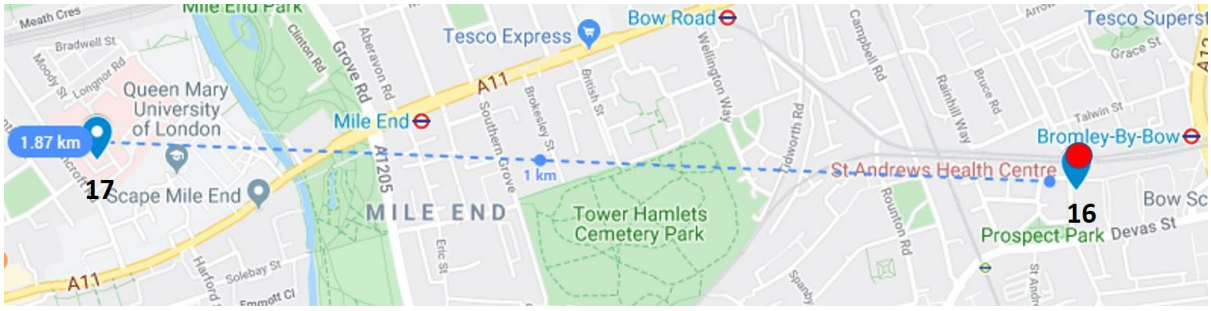


Figure 8: St Andrews' Health Centre and associated linked practice

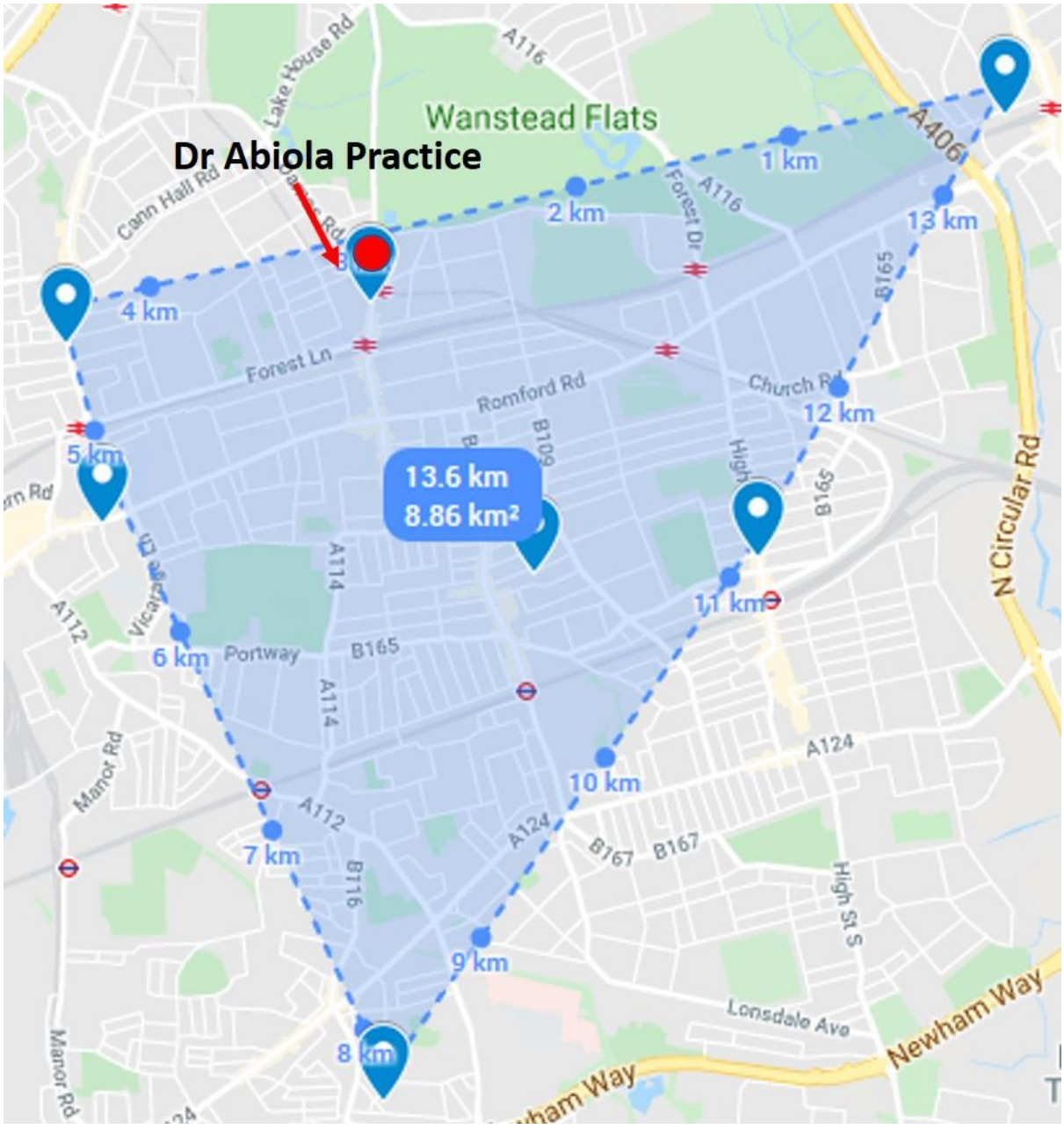


Figure 9: Dr Abiola Practice and associated linked practices

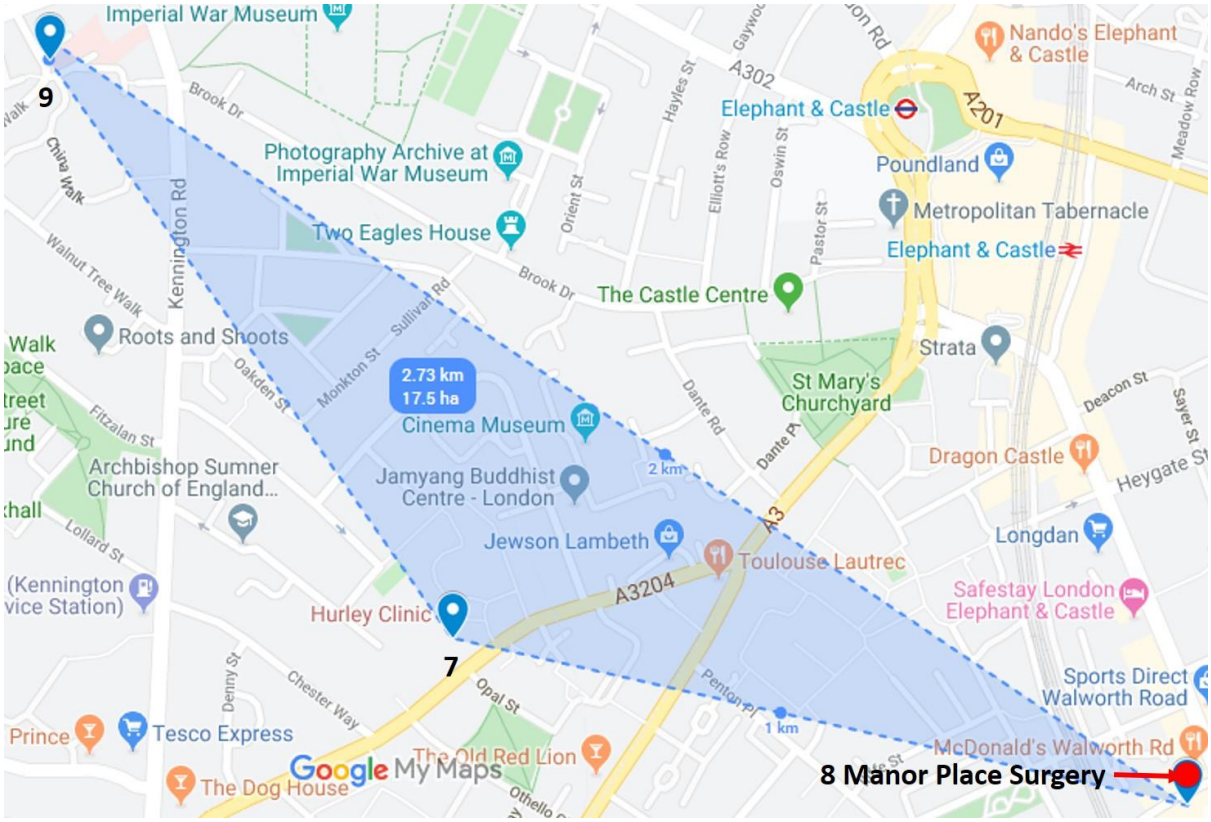


Figure 10: Manor Place Surgery and associated linked practices

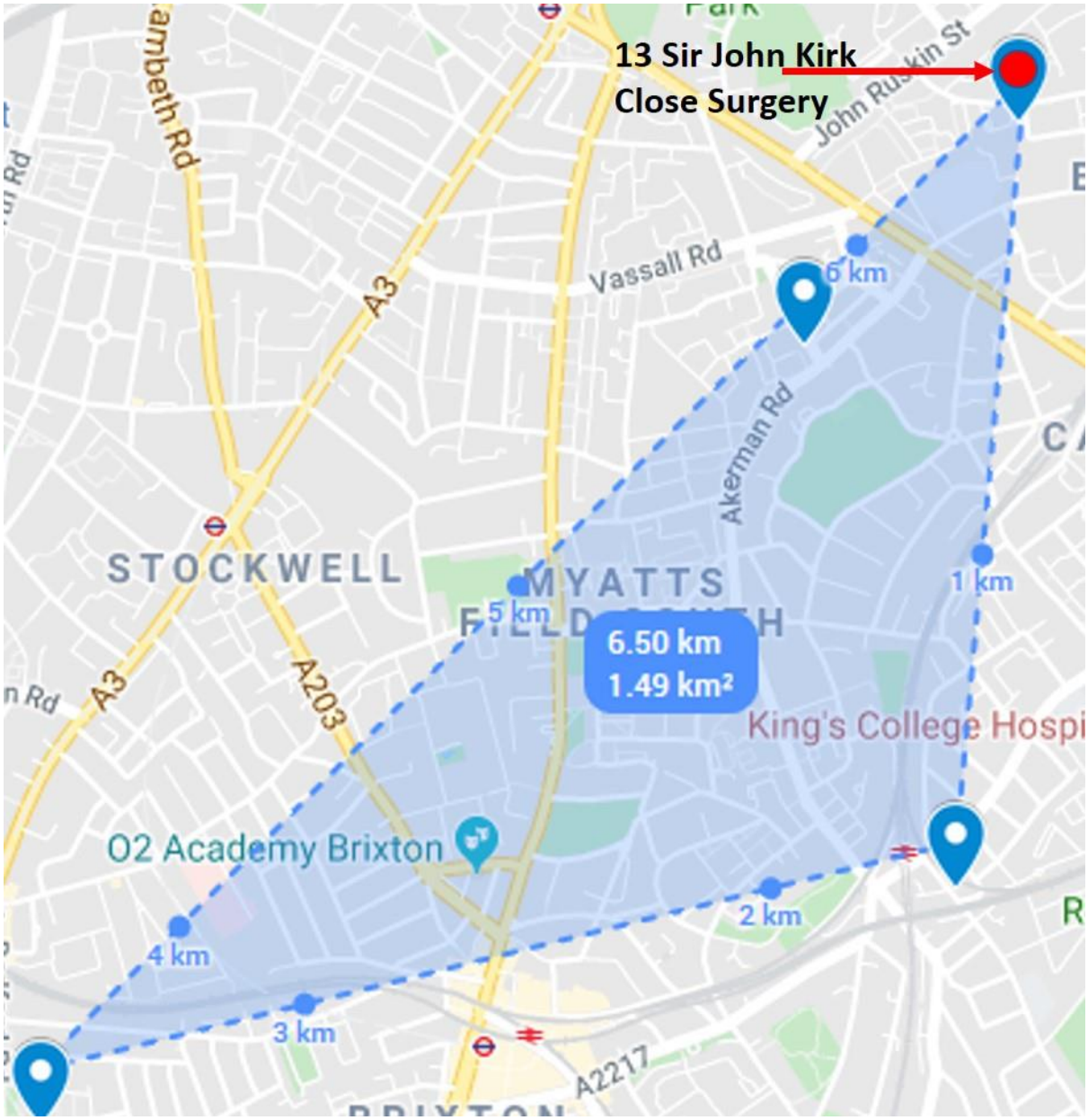


Figure 11: Sir John Kirk Close Surgery and associated linked practices

2.4.2 Follow-up for Positive Patients

2.4.2.1 Standard Operating Procedures

To ensure a consistent approach to the delivery of care, I wrote standard operating procedures (SOPs) for the provision of community based care by the Viral Hepatology services in East London and South London. SOPs are stepwise instructions on the execution of complex but routine services within healthcare. They aim to maintain quality by adhering to local and national guidelines, and provide uniformity of care regardless of which individual staff members are delivering the service. SOPs for East and South London services are found in appendices 9 & 10.

2.4.2.2 Referral process for patients testing positive in Primary Care

Patients who tested positive for HBsAg, HCV Ab or both were referred to their local hospital by clinical or administrative staff at the GP practice emailing an autopopulated referral letter to a dedicated HepFREE email address. The letter included patients details (name, address, date of birth), HepFREE screening test results, medication list and past medical history.

Referred patients were then booked into a dedicated HepFREE clinic list at either the RLH or KCH by myself.

2.4.2.3 Measurement of engagement and outcomes in HepFREE Follow-Up Trial

One of the primary objectives of the HepFREE study was to determine whether community based therapy is superior to conventional delivery of treatment as measured by engagement with management and treatment.

Engagement with the study was defined completion of at least three visits for diagnosis, investigation and management in a 12 month period:

- For patients who tested HBsAg positive, or HCV Antibody, RNA positive this was attending (i) diagnostic visit (i) prognostic investigation: ultrasound and/or Fibroscan® (iii) management visit
- For patients who tested HCV antibody positive or equivocal but HCV RNA negative, engagement was defined as attending the GP practice or the local hospital on two separate occasions.

Compliance with the clinical management plan was defined as attending at least one follow-up visit after the management plan was agreed by participant and clinicians.

Adherence to therapy in the study was defined as 80% completion of prescribed therapy.

The outcome of therapy was monitored. A successful outcome of therapy was defined as sustained viral response 12 weeks after treatment completion for HCV infected patients. The definition of successful outcome of therapy for HBV treatment was a reduction in viral load by >80% of starting value within 12 weeks.

Data relating to engagement, compliance with management plan and outcome of therapy was monitored until the end of data collection in February 2017 for all patients that screened positive as part of Stage 1 of HepFREE. Due to due to rapid developments in treatment availabilities for hepatitis C and changes in NHS policy, with regards to prescribing new hepatitis therapies, the 'clinical management plan' for some patients was variable throughout the course of the trial. Continuing to collect outcome data for all HepFREE patients that screened positive until Feb 2017 enabled the collection of 'adherence to therapy' and 'outcome of therapy' information for patients whose treatment options changed during the trial period.

Patients who were randomised to community care continued to receive their hepatology care, if appropriate, in the community until the HepFREE data collection stopped in February 2017. This was to allow the patients enough time to adjust to their treatment regimes in the community before moving their care back to 'standard of care' based at the local hospital once their study visits have been completed.

2.4.2.4 Supplementary consent to participating in HepFREE Follow-Up Trial

Patients testing positive for viral hepatitis were invited to participate in stage 2 of the HepFREE trial at their diagnostics appointment. The patients were provided with a detailed information sheet explaining the follow-up phase of the trial, enabling participants to make an informed decision as to whether they would like to remain in the trial or not. They were then asked to provide supplementary written consent to further participation. Consent was obtained by a GCP trained viral hepatology specialist who was blinded to the cluster randomisation of the patient's referring GP practice.

2.4.2.5 Patient Information Leaflet for HepFREE Follow-Up Trial

The patient information sheet did 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, and explained the follow-up visits in community and standard care. A copy of the Patient Information leaflet is found in Appendix 5.

2.4.2.6 Process of taking consent

The healthcare professionals who consented eligible patients for the HepFREE Follow-Up trial at their diagnostic out-patient appointment (in North East and South East London this was a delegated member of the local Hepatology Research team), were not aware of the patient's practice's allocation at the time when consent was sought. In general, this investigator was a local specialist hepatology nurse who had received GCP training and was on the HepFREE delegation log but not involved in provision of care for HepFREE patients. This individual was blinded to the allocation of the referring GP practice cluster randomisation, and therefore bias to recruitment of one or either arm of the trial could be minimised.

After joining the HepFREE trial team in August 2015 I started the process of setting up community-based follow-up clinics. Therefore from this point I was no longer blinded to allocation of referring GP practice cluster randomisation and so I trained local specialist hepatology research nurses at the RLH (North East London) and KCH (South East London) in taking consent for the HepFREE follow-up trial. This training involved a one hour session outlining the aims and objectives of the HepFREE Screening and Follow-Up Trials, reviewing the Follow-up Trial consent form and discussing questions patients may have regarding the consent process.

During the consent process, the participant was informed that if they chose to continue in the trial they would be randomised to receive monitoring and/or treatment for viral hepatitis (if required), at all subsequent follow-up appointments either in hospital (standard care) or in the community. Prior to giving consent, participants were provided with a further information leaflet which outlined the nature of the HepFREE Follow-Up trial and randomisation to community or hospital care. 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. For participants randomised to standard care follow-up, all appointments were based in the Hospital out-patients department.

Participants that consented to take part in the HepFREE follow-up trial, were subsequently informed of their treatment/monitoring allocation by the Viral Hepatology Specialist (VHS) who managed their treatment/active monitoring. For London participants, this VHS was myself as London Clinical Research Fellow.

Those participants who declined to participate in follow-up trial randomisation were followed up in standard care, however as per their previous consent to the HepFREE screening trial, their data would still be collected to form part of the Follow-Up Trial analysis.

Treatment allocation was concealed until after consent to participate in the trial was been obtained, in an effort to prevent bias between recruitment into the two arms of the trial (community vs hospital care). Patients were explicitly informed of their right to withdraw from the study if they were not comfortable with their treatment allocation at any point. If a participant subsequently withdrew consent to the trial completely, they were to be treated as per standard of care and data would be no longer be collected.

Follow-Up consent to remain on the study was sought at the first visit to secondary care subsequent to a referral. However, consent could also be sought at the subsequent visit to secondary care (e.g. the management planning visit) only if conditions did not allow for the consent to be sought at the first visit to the local hospital (e.g. no specialist nurse with GCP training was available). It was a pre-requisite that the consent must be stated (written) prior to the patient adopting their trial allocation (community care Vs standard (hospital) care).

The consent form was approved by the Research Ethics Committee as part of version 7.0 of the HepFREE Trial protocol (submitted 12 March 2015 and acknowledged 05 May 2015). A copy of the consent form can be found in Appendix 8.

2.4.3 HepFREE Clinics in Secondary Care

The HepFREE clinics at the Royal London Hospital and at King's College Hospital were new services set up in addition to and as part of the already well-established viral hepatitis outpatients clinics at both sites. As the London HepFREE CRF I was the HepFREE Viral Hepatitis Specialist (VHS) clinician at both sites. Clinics appointments were on set days of the week (Wednesday afternoons for RLH and Friday afternoons for KCH).

2.4.3.1 Diagnostics Appointment

At both sites, positive patients would be given an initial 30 minute appointment (diagnostic visit) to be seen by me. At this appointment, the patient's relevant history would be reviewed, past medical history discussed, medications reviewed, allergies noted and an abdominal examination performed. History and findings were documented on the patient's electronic health record (EPR) at the hospital (Cerner Millennium EPR at RLH and Sunrise EPR at KCH).

Onsite phlebotomy for baseline bloods test including full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFTs), coagulation screen, International Normalised Ratio (INR), full blood-borne virus screen (including HBsAg level, e-antigen, e-antibody, core-antibody, HCV Ab and RNA if needed and HIV Ab) and other liver markers such as immunoglobulins, caeroplasmin and alpha-fetoprotein were performed.

The patient was invited to participate in the HepFREE Follow-Up trial and was asked to provide written consent to be randomised by cluster-based approach to either secondary or community care. As CRF I was aware of the randomisation outcome for each patient (as this was traceable to their referring GP practice), and so consent was performed by a local specialist nurse with GCP training in asking for research consent.

2.4.3.2 Prognostic and Imaging Appointments

The patient would then be referred for transient elastography (also known as Fibroscan®) and ultrasound to allow imaging of the liver and assessment of fibrosis/cirrhosis (severity of disease assessment).

At KCH, Fibroscan® was usually performed by a specialist nurse on the same day as the initial appointment, with ultrasound being performed by a sonographer during a dedicated liver clinic list on the same day as the follow-up (management) appointment.

At the RLH, Fibroscan® and ultrasound were performed separately to the outpatients clinics but completed by the time of the next follow-up (management appointment).

2.4.3.3 Multi-Disciplinary Team Meetings and Operational Delivery Networks

At both hospitals, between the initial diagnostics and prognostics visit and the management visit, patients were discussed at the local Viral Hepatitis Multi-disciplinary meeting, which was attended by Consultant Hepatologists, specialists pharmacists, HIV Physicians and Virologists, Hepatology trainees, and specialist nurses from various local sites.

The recommendations made by the MDT also acted as the recommendations of the local Operational Delivery Network (ODN) who would approve new directly acting antivirals (DAA) therapies for Hepatitis C positive patients. ODNs are the structures through which hepatitis C treatment is England has been delivered since 2015. The networks involve regional centres which manage treatment decisions and prescribing, and which have a dispersed treatment model which aims to support partnership working and access for local patients.

The RLH ODN is the hub of the London North East network and named lead is Prof Graham R. Foster (Professor of Hepatology at QMUL). The KCH ODN is the hub of the South Thames Hepatitis Network and named lead is Dr. Kosh Agarwal (Consultant Hepatologist at KCH).

2.4.3.4 Management Visit

At the patient's management visit (usually scheduled 4-8 weeks following their initial appointment) they were advised of their baseline results, the outcome of their randomisation to either hospital or community based follow-up and their individual management plan (active monitoring or treatment) would be discussed and agreed with the patient.

If the patients were randomised to hospital care, they would be given up a follow-up appointment within 3 months.

For those patients randomised to community based care, their details were noted (including a contact phone number) and advised they would be given a date for their community-based follow-up appointment at their particular practice which would be within 3 months.

If patients declined to consent to the HepFREE Follow-Up randomisation, follow-up defaulted to secondary care.

2.4.4 HepFREE Community Clinics

2.4.4.1 Arranging Community Clinic Appointments

The next steps were to arrange a suitable clinic day at the designated community practice. Follow-up appointments were located at a practice near to the patient's original screening practice – in some cases this was the same practice, in others it was a nearby practice. In all cases, the community clinic was closer to the patient's home address at the time of screening than the local hospital. When patients had consented to community follow-up, the local GP practice managers were contacted in order to arrange a suitable date for a viral hepatitis follow-up clinic at the practice.

The main challenge at each practice was finding a spare room suitable to use for the HepFREE Viral Hepatitis Clinic. Each practice usually had a spare room on a particular session (morning or afternoon) on a particular day of the week and was happy for the HepFREE team to use the room at this time. A computer was not required as notes from the consultations were documented on the local hospital EPR system shortly after the clinic rather than on the local GP EMIS system. As VHS, I also took my own phlebotomy kit (disposable needles with vacutainers, alcohol wipes, gauze

plasters and tourniquet) and blood bottles (for virology, biochemistry and haematology samples) from the local hospital.

As there were small numbers of positive patients randomised to each practice, patients were asked by telephone to attend on the day and time when a practice room was free. Most patients were agreeable to these set days, however a small number of patients requested specific times or days to be seen – they felt they would be unable to attend at other times due to work or family commitments. The HepFREE Community Clinic practices and myself were in each case able to arrange a mutually suitable time and day for the patients to be seen. However this was in contrast to those patients who were randomised to hospital follow-up who were asked to attend on specific clinical days at each site.

Patients were notified of their community clinic appointment dates by telephone call and by letter from the referring hospital. The community GP practice played no role in contacting the patients – this was because many of the patients were not being seen at the practice where they were registered. Subsequently, none of the community clinic patients received a reminder text as they would have done for either a standard hospital appointment or a standard GP appointment. Therefore, this group of patients were phoned 48 hours prior to their appointment by me as a reminder.

2.4.4.2 Follow-Up Visits

At both the community clinic and standard hospital appointments patients' histories were reviewed and management plan followed. For those patients who were being monitored (for example those who were HBeAg negative chronic infection HBV) blood tests and six-monthly ultrasound HCC scanning was arranged. Patients were follow-up on a 3-6 monthly basis. For those patients starting HBV or HCV treatment, the agreed treatment (from the ODN) was issued at the hospital pharmacy and transported by the VHS to the community practice. Any bloods taken at the community practice were transported back to the local hospital either by me or by courier (with arrangement with the practice).

At both hospital and community based clinics, patients' blood and imaging results were checked by myself within 7 days and a letter issued to the patient and their GP of the findings, management plan and date and location for the next appointment.

Patients on HBV monitoring were seen 4 times within 12 months and then 6 monthly.

Patients attending secondary care follow-up may also have been offered liver biopsy and participation in a research trial. This is because this cohort of patients was offered standard of care management. No community follow-up patients entered other research trials during the HepFREE period.

2.4.5 Treatments Offered in HepFREE Follow-Up Clinics

HBV Treatment

All patients with chronic HBV infection were assessed for the degree of disease activity in line with standard practice. Patients with active disease starting HBV treatment in London were all commenced on interferon-free regimens with third generation oral once-daily antiviral agents (either tenofovir or entecavir) and reviewed at one month after commencing therapy (for bloods including full blood count, U&E, LFTs and HBV DNA levels plus urinalysis) and then again for the same tests at 3 months and 6 months. Adherence was monitored at each visit and viral suppression was defined as a fall in DNA level of 80% or more from the baseline.

HCV treatment

All patients with chronic HCV infection underwent an assessment of the degree of liver fibrosis (either by liver biopsy or Fibroscan®) and were offered treatment in accordance with NHSE and NICE guidelines.

For patients treated for Hepatitis C, during the early stages of the HepFREE trial period (March 2014-Jan 2015), interferon-free therapies were not widely available for prescription on the NHS. Access to therapy was also dependent on disease stage and HCV genotype. Therefore patients were offered treatment with interferon-based therapies, or the option to await DAAs (which were deemed to be likely to be available within a few months).

From the initiation of HepFREE screening trial at the first group of intervention practices in March 2014 until September 2016, treatment for patients with genotype 1 HCV was with sofosbuvir/ledipasvir and treatment for patients with genotype 3 and cirrhosis was with pegylated interferon, ribavirin and sofosbuvir. All other patients with genotype 3 HCV were offered therapy with pegylated interferon and ribavirin and given the option of delaying therapy until all oral DAA agents were approved and funded by NHSE. From September 2016 until study recruitment closure in February 2017 patients with Genotype 1 HCV were offered paritaprevir, ombitasvir and dasabuvir and all patients with genotype 3 HCV were offered sofosbuvir/velpatasvir.

Patients commencing HCV Interferon based therapy were reviewed at Weeks 2,4,8,12, 16, 20, 24, 28, 36 and 48. Patients commencing DAAs for HCV treatment were reviewed at weeks 1,2,4,8,12,16 and 24. Adherence to therapy was monitored at each visit and viral suppression was defined as achieving SVR12 (for DAAs) or SVR24 (for interferon based therapy).

Table 7 Treatment for viral hepatitis for London patients in the HepFREE trial

Time period	**Virus**					
	HBV	**HCV G1**	**HCV G2**	**HCV G3**		**HCV G4**
				No Cirrhosis	**Cirrhosis**	
March 2014- Sept 2016	NRTIs	Sofosbuvir and Ledipasvir	PEG-IFN, Await DAAs or Research trials	PEG-IFN and Ribavirin or await DAAs	PEG-IFN, Ribavirin, Sofosbuvir	PEG-IFN, Await DAAs or Research trials
Sept 2016 – Feb 2017	NRTIs	Paritaprevir, Ombitasvir and Dasabuvir	PEG-IFN, Await DAAs or Research trials	Sofosbuvir and Velpatasvir	PEG-IFN, Ribavirin, Sofosbuvir	PEG-IFN, Await DAAs or Research trials

2.4.6 Analysis of London Community Clinic Outcomes

Data collected in the OpenClinica platform regarding follow-up engagement and treatment was collated in Microsoft Excel and descriptive and exploratory analysis performed using this program. Further statistical analysis was performed using Stata version 14.

2.5 Patient Pre-Screening Survey

As part of the HepFREE study, in 2014 a pre-screening survey of patients eligible for viral hepatitis screening was performed by the qualitative researcher John Owiti. The survey was designed by the HepFREE Research team (including Prof Foster and John Owiti) and Owiti collected the data. I data cleaned the 2014 data and linked it to the HepFREE screening outcomes. I also undertook original analysis of the data.

A subset of potential participants from interventional screening practices in North East London, South East London and Bradford were identified using the bespoke HepFREE eligibility searches run on Primary Care electronic patient records. This subset of patients formed the sample for a population based survey of eligible patients in order to assess the characteristic of individuals who accept or decline at all stages of the trial.

Potential participants were contacted by letter of invitation, with further information detailing the project (in English or appropriate translation), including the voluntary nature of involvement, and a choice of mode of participation by either (1) telephone, (2) face-to-face interview, or (3) postal survey completion. Two weeks after initial contact, potential participants were contacted by the GP practice, via telephone (up to 3 times) to confirm if they received the letter and whether they have any questions for the GP or the research team, indicating that they were happy to continue and participate.

For those participants indicating a willingness to participate by phone, verbal consent was sought in the presence of a witness, with appropriate language translation (as required) and documented. Those indicating a preference for completion by post had all documents with instructions forwarded to them with a self-addressed envelope with a contact telephone number for any enquiries. Finally, individuals requesting face-to-face interview were invited to attend an appointment at their host GP surgery with appropriate language translation (as required) to complete the survey. It was highlighted to participants that involvement was voluntary and the interview could be stopped at any time, if a participant did not wish to continue. The interview was concluded with a documented verbal consent.

The patients were asked about their illness perceptions and narratives (explanatory models) about hepatitis using an adapted version of the Barts Explanatory Model Interview checklists. These were developed from focus groups and literature review information, following the methods set out in the original development for use in common mental disorders. Two other validated patient-reported

outcomes were completed by interview: patient health questionnaire (PHQ-9) and the generalized anxiety disorder 7-item (GAD-7) scale.

Data collected from the pre-screening database was linked, using the pseudonymised identifier generated by the GP database, to HepFREE data collected as the part of the screening trial. This was to ascertain whether there are certain beliefs of perceptions about hepatitis that indicate whether a patient is more or less likely to screen for viral hepatitis when offered a screen.

2.5.1 Data processing and analysis

Survey data were initially gathered by completion of paper questionnaires and then manually uploaded to the OpenClinica database by John Owiti. I cleaned the data completing an "other" entry for any question responses that were not completed (i.e. left blank).

Outcomes of the data were then collated by myself with the assistance of a Barts Health Gastroenterology Fellow and analysed by myself and a statistician from the Centre of Psychiatry, Wolfson Institute of Preventive Medicine, Queen Mary University of London, using version 14 of the statistical software Stata.

2.6 HepFREE Provider Experience Substudy

2.6.1 Study Design

My HepFREE Provider Experience substudy was a Qualitative Research Study which was designed to investigate the barriers and facilitators to offering testing for viral hepatitis in primary care, as perceived by the healthcare providers who participated in the HepFREE trial. This followed on from qualitative research performed by Sweeney et al in 2014 prior to the launch of the HepFREE screening trial, which interviewed key informants, patients and general practitioners regarding the implementation and running of the HepFREE trial in practice. (132) I wanted to expand on one aspect of this work in order to understand the views of general practitioners over an extended period of time from the early stages of trial implementation and after closure of recruitment to the HepFREE screening trial. I also wanted to collect the views and experiences of other members of the Primary care practice teams who were involved in the HepFREE trial, including Primary Care Nurses and administrative and reception staff.

2.6.2 Identifying Practices and Interviewees

In my HepFREE Provider Experience substudy I, interviewed 1-2 members of the practice healthcare staff groups, at 12 practices (out of 50 intervention practices). The staff members included general practitioners, practice nurses, healthcare assistants and healthcare administrators or practice managers. I completed the interviews with the support of another independent researcher Dr Dania Shoeb. The focus of the interviews was to explore the views of healthcare professionals in their experience of running a large trial testing for viral hepatitis, and to assess their attitudes to viral hepatitis testing in primary care following completion of the trial.

These practices were purposively sampled based on their hepatitis screening rates in the HepFREE study, and their location. (167) Practices were divided into high performers (screening more than 20% of eligible patients), low performers (less than 10% of those eligible) and intermediate performers (10-20%).

All interviewees were adult healthcare workers, interviews were semi-structured, allowing the researchers to ask open-ended questions which may lead to further exploration of a specific topic. (168) The interview method of qualitative research has been used with both patient groups and healthcare professionals in regards to provider experiences and perspectives on delivering screening and treatment interventions for HIV and sexually transmitted infections in primary care settings, but this is the first time this methodology has been used for in viral hepatitis screening in primary care. (169–171)

Along with Dr Shoeb, I conducted the interviews in person, or by telephone between November 2016 and February 2017. All interviews were audio-recorded (with consent) on dictaphone and transcribed verbatim. Any identifiable data was anonymised during transcription. No patient data was recorded for this study. Both researchers had no previous direct contact with their allocated primary care practices.

An interview topic guide was prepared with the assistance and advice of Dr Moira Kelly and Dr Lorna Sweeney, that aimed to be open-ended, neutral, sensitive and clear to the interviewee. (168,172) The initial pre-trial interviews focussed on setting up and implementing a viral hepatitis screening trial. For my follow-up qualitative study, I was interested in staff perception of the trial process and outcomes at the end of the testing period.

I wanted to understand the motivations and challenges of running a screening programme (perceived benefits to patients and to practice, impact on time and resources, impact of payment and the prioritisation of the study in a busy practice), the practical implications of being involved in a research study (local trial training, use of trial dataset) and the challenges of recruiting and consenting patients to the trial and therefore the interview questions were designed to explore these issues (see Appendix 14 for the interview questions).

Interviewees were contacted initially by email and supplied with a written information leaflet and asked to provide written consent at the time of the interview (see appendices 12 and 13). Interviewees were asked for written consent to link answers from the 2014 study to the new study where applicable.

Interviews were performed by myself and Dr Dania Shoeb, a GP trained in Qualitative Research. Both interviewers had no previous direct contact with their allocated primary care practices. All interviews were audio-recorded (with consent) on dictaphone and transcribed verbatim. Any identifiable data was anonymised during transcription. No patient data was recorded for this study. Thematic analysis was used to identify important commonalities and differences within provider accounts.

The interview data was analysed using a framework method, and findings were interpreted in light of the thematic framework from the 2014 dataset.

2.6.3 Data Analysis

Datasets from the 2017 interviews were analysed using the Framework method. The Framework method is widely used by qualitative researchers and is a matrix based analytic method. The thematic framework is used to classify and organise data according to key themes, concepts and categories. Therefore the outcomes of the study can be comprised of main themes with related subtopics.

The process of framework analysis is made up of five steps (173):

(i) Familiarisation
(ii) Thematic framework identification
(iii) Indexing
(iv) Charting
(v) Mapping and interpretation

The themes and subtopics evolve and are refined through familiarisation with the data and cross-sectional labelling.

My analysis process involved the transcription of all interviews in word documents to familiarise myself with the raw data. After printing out the interviews, I then read through each interview several times, both in linear form and again in parallel with the other interviews. During this reading process I used highlighter markers and margin notes to identify key themes and ideas from each interview response, which formed a framework. On reviewing these notes I charted each theme within a Microsoft Excel spreadsheet with each theme and subtopic allocated a row and each respondent a column. I then used the transcriptions to collate data from each interview into the appropriate theme and subtopic, to build a framework with themes and subthemes.

I then reviewed the 2014 interviews framework analysis. As the 2016-2017 interviews were following up with healthcare staff on the same project at different time points, I looked to analyse both sets to expand upon the emergent themes.

2.6.4 Ethics Approval

This 2014 early trial primary care staff interviews research study was approved by the Research Ethics Committee at Queen Mary, University of London (No. QMREC2012/02). After discussing with the Queen Mary Research Ethics Committee team it was felt that the 2017 substudy is intrinsically linked to the main HepFREE study and would be best placed seeking ethical approval as an amendment to the study protocol, rather than as a separate research study via QMREC. Ethics approval was given by the HRA Research Ethics Committee on 21st October 2016.

3. Results: HepFREE Trial Results

3.1 Introduction

The results of the HepFREE screening trial as published are presented here. The data from Bradford, London and Oxford were merged by the statistician and are presented here to provide a complete picture of the trial. As previously noted the data in Bradford and Oxford were collected by others and my role for these sites was to clean the data. The London data was, chiefly, collected by me. Data analysis was performed by myself and the trial statistician – I provided the clinical oversight, worked to define which data should, or should not be included, and discussed with the statistician the analyses that were to be performed. The write up of the data for the published manuscript was completed by myself with assistance from Prof. Foster

3.2 Screening Outcomes

Recruitment and testing ran from Feb 7th 2014, to Feb 4th 2017, and each practice recruited for 18 consecutive calendar months. In a parallel, observational study we examined the impact of screening in area of low immigrant diversity (Oxford). In nine Oxford practices, recruitment and testing ran from May 22, 2015, to April 16, 2017, and each practice recruited for 18 consecutive calendar months.

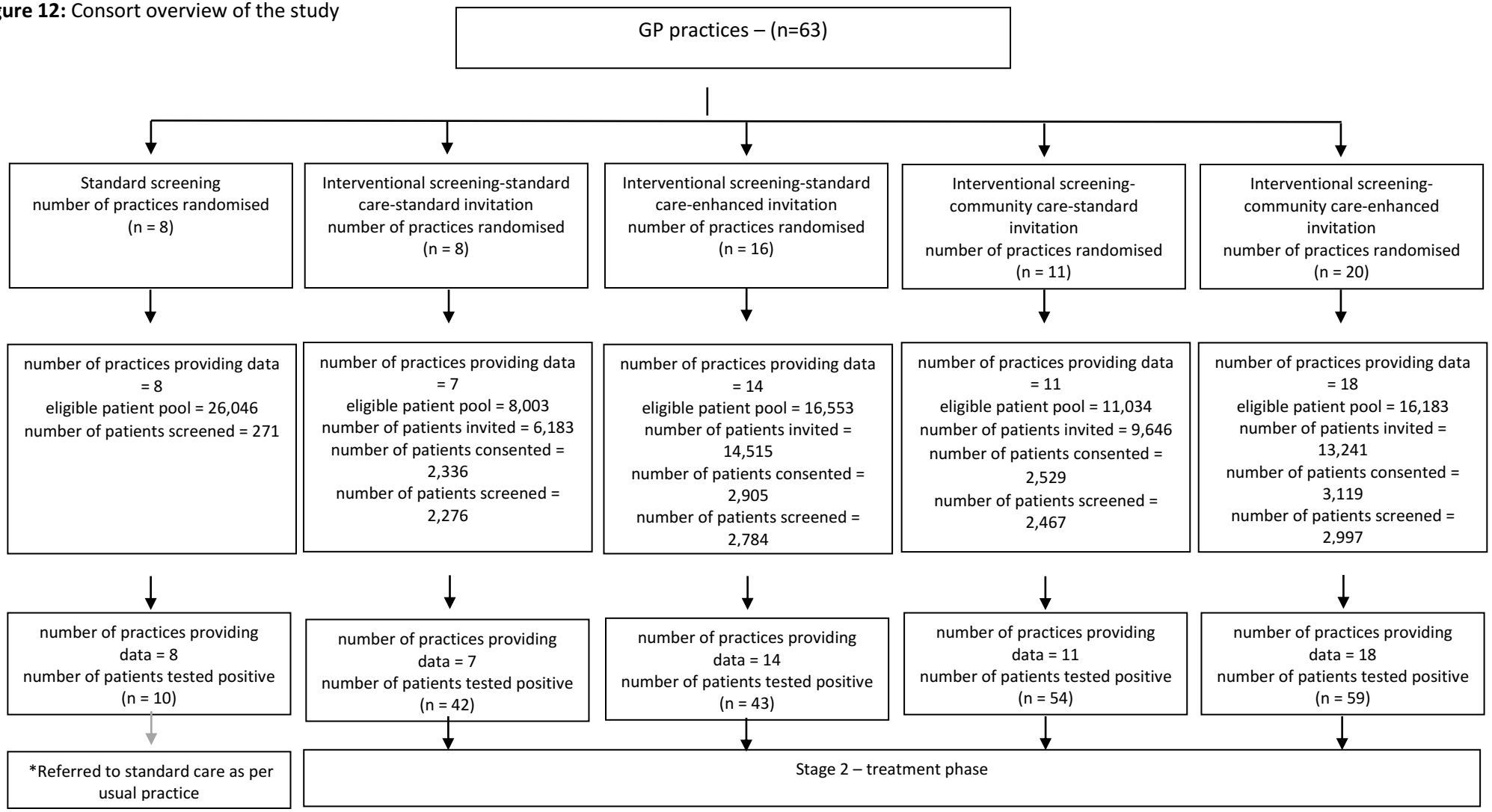
For the main study we approached 70 general practices in three areas with a high density of migrants, of which 63 general practices agreed to participate. Five practices withdrew before contributing data and 58 practices were randomly assigned to groups: eight practices were allocated to the control group, in which no intervention beyond a single teaching session was given to GPs, and 50 practices were allocated to receive an intervention, in which doctors were given a financial incentive and patients received a combination of a standard or enhanced letter and hospital-based or community care. 15 intervention practices were asked to invite all eligible patients (which were referred to as uncapped) and 35 intervention practices were capped to only approach 500 eligible patients for screening. 31 738 patients were assessed in the control practices, including 26 046 (38·4%) patients who were deemed eligible of 67 820 patients who were originally registered and 5692 new patients, and 58 512 patients from the interventional groups were assessed, including 51 773 (14·7%) patients who were deemed eligible of 351 710 patients (some of whom had been randomly selected from a pool of 152 321 eligible, initially registered patients) and 6739 new patients.

These patients were determined to be eligible for testing when assessing electronic records and at registration of new patients.

In Oxford, nine general practices comprising a total of 105,714 registered patients, were asked to test a total of 6,854 people (5022 registered and 1832 new registrants) and were paid for so doing. Testing rates were lower (515 of 6854, 7.5%) than those seen in areas of high immigrant density. seven (1·4%) patients positive for HBsAg and none for HCV Ab. There was no further analysis of engagement in the Oxford cohort.

The flowchart of the 63 practices is shown in Figure 12, with the characteristics of all 63 practices and of the 58 practices who provided data for the main study are shown in Tables 8 and 9.

Figure 12: Consort overview of the study



*GP practices allocated to standard screening arm do not take part in stage 2 of this trial

Table 8: Characteristics of the 63 invited practices.

Characteristics	Standard screening (n = 8)	Interventional screening				Total (n = 63)
		Standard care-standard invitation (n = 8)	Standard care-enhanced invitation (n = 16)	Community care-standard invitation (n = 11)	Community care-enhanced invitation (n = 20)	
Site						
Bradford	3	2	6	2	8	21
east London	3	2	7	5	5	22
South London	2	4	3	4	7	20
Number of eligible patients						
less than 1600	1	1	7	4	8	21
1600 – 3300	5	2	7	5	10	29
More than 3300	2	5	2	2	2	13

Table 9: Characteristics of the 58 practices providing data

Characteristics	Standard screening (n = 8)	Interventional screening				Total (n = 58)
		Standard care-standard invitation (n = 7)	Standard care-enhanced invitation (n = 14)	Community care-standard invitation (n = 11)	Community care-enhanced invitation (n = 18)	
Site						
Bradford	3	2	6	2	8	21
East London	3	2	5	5	5	20
south London	2	3	3	4	5	17
Number of eligible patients						
less than 1600	1	0	5	4	7	17
1600 – 3300	5	2	7	5	9	28
more than 3300	2	5	2	2	2	13

The characteristics of the patients by randomised groups is shown in Table 10. A total of 90,250 participants in 58 practices were included in the main HepFREE trial, 31,738 in the 8 control arm practices and 58,512 in the 50 intervention arm practices. The majority, 77,819, were registered in the practices at the start of the study. The rest were patients who registered with the practices during the 18 month period of the study. Within the intervention arm I have shown characteristics of participants in the four separate randomised groups for completeness. The tables show even matching of the different groups. Recording of first and second generation immigrants was very poor and within the practices and analysis by this metric was not possible.

Participation in screening for viral hepatitis.

In the eight standard screening practices, 543 participants were screened and in the 50 interventional screening practices, 47,883 were invited for screening and 11,386 were screened. Tables 13a, 13b and 13c show the characteristics of these participants.

Table 10: Characteristics of all participants in study practices by randomisation group

Characteristics	Standard screening (n = 31,738)		Interventional screening								Total (n = 90,250)	
			Standard care-standard invitation (n = 8,501)		Standard care-enhanced invitation (n = 19,192)		Community care-standard invitation (n = 11,769)		Community care-enhanced invitation (n = 19,050)			
	No	%	No	%	No	%	No	%	No	%	No	%
Gender												
Female	16,549	52.1%	4,241	49.9%	10,283	53.6%	5,927	50.4%	9,736	51.1%	46,736	51.8%
Male	15,189	47.9%	4,260	50.1%	8,908	46.4%	5,842	49.6%	9,314	48.9%	43,513	48.2%
Missing	-	-	-	-	1	0.0%	-	-	-	-	1	0.0%
Ethnicity												
Black	3,142	9.9%	847	10.0%	2,141	11.2%	1,966	16.7%	1,912	10.0%	10,008	11.1%
Bangladeshi	3,289	10.4%	419	4.9%	761	4.0%	1,112	9.5%	1,065	5.6%	6,646	7.4%
Indian	4,269	13.5%	420	4.9%	1,347	7.0%	575	4.9%	3,157	16.6%	9,768	10.8%
Pakistani	8,771	27.6%	5,057	59.5%	6,016	31.4%	2,573	21.9%	5,355	28.1%	27,772	30.8%
Other Asian	2,857	9.0%	216	2.5%	1,662	8.7%	873	7.4%	2,039	10.7%	7,647	8.5%
Eastern Caucasian	1,309	4.1%	301	3.5%	1,558	8.1%	378	3.2%	889	4.7%	4,435	4.9%
Other	8,101	25.5%	1,241	14.6%	5,707	29.7%	4,292	36.5%	4,633	24.3%	23,974	26.6%
Age (years)												
mean (sd)		38.0 (14.4)		39.2 (15.5)		38.4 (14.6)		39.9 (15.2)		37.8 (14.1)		38.4 (14.6)

Table 11: Characteristics of participants registered with study practices at the start of screening trial by randomisation group

Characteristics	Standard screening (n = 26,046)		Interventional screening								Total (n = 77,819)	
			Standard care-standard invitation (n = 8,003)		Standard care-enhanced invitation (n = 16,553)		Community care-standard invitation (n = 11,034)		Community care-enhanced invitation (n = 16,183)			
	No	%	No	%	No	%	No	%	No	%	No	%
Gender												
Female	13,351	51.3%	3,982	49.8%	8,860	53.5%	5,542	50.2%	8,164	50.4%	39,899	51.3%
Male	12,695	48.7%	4,021	50.2%	7,692	46.5%	5,492	49.8%	8,019	49.6%	37,919	48.7%
Missing	-	-	-	-	1	0.0%	-	-	-	-	1	0.0%
Ethnicity												
Black	2,619	10.1%	846	10.6%	1,927	11.6%	1,881	17.0%	1,796	11.1%	9,069	11.7%
Bangladeshi	2,837	10.9%	407	5.1%	735	4.4%	1,073	9.7%	933	5.8%	5,985	7.7%
Indian	3,506	13.5%	397	5.0%	1,241	7.5%	560	5.1%	2,745	17.0%	8,449	10.9%
Pakistani	7,874	30.2%	4,786	59.8%	5,697	34.4%	2,429	22.0%	4,785	29.6%	25,571	32.9%
Other Asian	2,376	9.1%	199	2.5%	1,276	7.7%	812	7.4%	1,622	10.0%	6,285	8.1%
Eastern Caucasian	965	3.7%	203	2.5%	1,267	7.7%	298	2.7%	663	4.1%	3,396	4.4%
Other	5,869	22.5%	1,165	14.6%	4,410	26.6%	3,981	36.1%	3,639	22.5%	19,064	24.5%
Age (years)												
Mean (sd)	38.8 (14.8)		39.3 (15.5)		39.2 (15)		40.2 (15.3)		38.5 (14.5)		39.1 (14.9)	

Table 12: Characteristics of participants who joined the study during the study period

Characteristics	Standard screening (n = 5,692)		Interventional screening								Total (n =12,431)	
			Standard care-standard invitation (n = 498)		Standard care-enhanced invitation (n = 2,639)		Community care-standard invitation (n = 735)		Community care-enhanced invitation (n = 2867)			
	No	%	No	%	No	%	No	%	No	%	No	%
Gender												
Female	3,198	56.2%	259	52.0%	1,423	53.9%	385	52.4%	1,572	54.8%	6,837	55.0%
Male	2,494	43.8%	239	48.0%	1,216	46.1%	350	47.6%	1,295	45.2%	5,594	45.0%
Ethnicity												
Black	523	9.2%	1	0.2%	214	8.1%	85	11.6%	116	4.0%	939	7.6%
Bangladeshi	452	7.9%	12	2.4%	26	1.0%	39	5.3%	132	4.6%	661	5.3%
Indian	763	13.4%	23	4.6%	106	4.0%	15	2.0%	412	14.4%	1,319	10.6%
Pakistani	897	15.8%	271	54.4%	319	12.1%	144	19.6%	570	19.9%	2,201	17.7%
Other Asian	481	8.5%	17	3.4%	386	14.6%	61	8.3%	417	14.5%	1,362	11.0%
Eastern Caucasian	344	6.0%	98	19.7%	291	11.0%	80	10.9%	226	7.9%	1,039	8.4%
Other	2,232	39.2%	76	15.3%	1,297	49.1%	311	42.3%	994	34.7%	4,910	39.5%
Age (years)												
Mean (sd)	34.3 (11.7)		37.5 (15)		33.7 (11.2)		35.3 (12.5)		33.8 (10.9)		34.2 (11.7)	

Table 13a: Characteristics of all eligible, invited, and screened participants.

Patient characteristics	Standard screening (number of practices = 8)				Interventional screening (number of practices = 50)					
	Eligible patient pool (n = 31,738)		Screened (n = 543)		Eligible patient pool (n = 58,512)		Invited for screening (n = 47,883)		Screened (n = 11,386)	
	No	%	No	%	No	%	No	%	No	%
Gender										
Female	16,549	52.1%	304	56.0%	30,187	51.6%	24,401	51.0%	6,537	57.4%
Male	15,189	47.9%	239	44.0%	28,324	48.4%	23,481	49.0%	4,848	42.6%
Missing	0	0.0%	0	0.0%	1	0.0%	1	0.0%	1	0.0%
Ethnicity										
Black	3,142	9.9%	112	20.6%	6,866	11.7%	6,153	12.9%	545	4.8%
Bangladeshi	3,289	10.4%	61	11.2%	3,357	5.7%	2,974	6.2%	905	8.0%
Indian	4,269	13.5%	25	4.6%	5,499	9.4%	4,563	9.5%	1,148	10.1%
Pakistani	8,771	27.6%	38	7.0%	19,001	32.5%	15,570	32.5%	6,814	59.9%
Other Asian	2,857	9.0%	55	10.1%	4,790	8.2%	3,656	7.6%	350	3.1%
Eastern Caucasian	1,309	4.1%	9	1.7%	3,126	5.3%	2,213	4.6%	406	3.6%
Other	8,101	25.5%	243	44.8%	15,873	27.1%	12,754	26.6%	1,218	10.7%
Age (years)										
mean (sd)	38.0 (14.4)		35.7 (10.9)		38.6 (14.7)		39.1 (14.9)		43.5 (15.4)	

Table 13b: Characteristics of eligible, invited, and screened participants registered with study practices at the start of trial by randomisation group.

Patient characteristics	Standard screening				Interventional screening					
	Eligible patient pool (n = 26,046)		Screened (n = 271)		Eligible patient pool (n = 51,773)		Invited for screening (n = 43,585)		Screened (n = 10,524)	
	No	%	No	%	No	%	No	%	No	%
Gender										
Female	13,351	51.3%	142	52.4%	26,548	51.3%	22,131	50.8%	6,059	57.6%
Male	12,695	48.7%	129	47.6%	25,224	48.7%	21,453	49.2%	4,464	42.4%
Missing	-	-	-	-	1	0.0%	1	0.0%	1	0.0%
Ethnicity										
Black	2,619	10.1%	67	24.7%	6,450	12.5%	5,873	13.5%	537	5.1%
Bangladeshi	2,837	10.9%	47	17.3%	3,148	6.1%	2,821	6.5%	821	7.8%
Indian	3,506	13.5%	13	4.8%	4,943	9.5%	4,251	9.8%	1,024	9.7%
Pakistani	7,874	30.2%	24	8.9%	17,697	34.2%	14,402	33.0%	6,414	60.9%
Other Asian	2,376	9.1%	28	10.3%	3,909	7.6%	3,180	7.3%	324	3.1%
Eastern Caucasian	965	3.7%	1	0.4%	2,431	4.7%	1,869	4.3%	306	2.9%
Other	5,869	22.5%	91	33.6%	13,195	25.5%	11,189	25.7%	1,098	10.4%
Age (years)										
mean (sd)	38.8 (14.8)		38.6 (12.2)		39.2 (15)		39.5 (15.1)		43.9 (15.4)	

Table 13c: Characteristics of eligible, invited, and screened participants who joined the trial during the study period

Patient characteristics	Standard screening (number of practices = 8)				Interventional screening (number of practices = 15)					
	Eligible patient pool (n = 5,692)		Screened (n = 272)		Eligible patient pool (n = 6,739)		Invited for screening (n = 3,944)		Screened (n = 862)	
	No	%	No	%	No	%	No	%	No	%
Gender										
Female	3,198	56.2%	162	59.6%	3,639	54.0%	2,097	53.2%	478	55.5%
Male	2,494	43.8%	110	40.4%	3,100	46.0%	1,847	46.8%	384	44.5%
Ethnicity										
Black	523	9.2%	45	16.5%	416	6.2%	277	7.0%	8	0.9%
Bangladeshi	452	7.9%	14	5.1%	209	3.1%	149	3.8%	84	9.7%
Indian	763	13.4%	12	4.4%	556	8.3%	287	7.3%	124	14.4%
Pakistani	897	15.8%	14	5.1%	1,304	19.4%	865	21.9%	400	46.4%
Other Asian	481	8.5%	27	9.9%	881	13.1%	465	11.8%	26	3.0%
Eastern Caucasian	344	6.0%	8	2.9%	695	10.3%	343	8.7%	100	11.6%
Other	2,232	39.2%	152	55.9%	2,678	39.7%	1,558	39.5%	120	13.9%
Age (years)										
mean (sd)	34.3 (11.7)		32.8 (8.7)		34.2 (11.6)		34.3 (11.5)		38.6 (13.6)	

Screening rates for viral hepatitis by age and ethnicity are shown in Tables 14a, 14b and 14c. These overall screening rates were more than 10 times higher in the interventional screening practices but there was considerable variaiton by age and ethnicity. Screening rates were higher in women than in men. respectively.

Table 14a Screening rates for viral hepatitis by ethnicity, gender and age in all participants

	Standard screening			Interventional screening		
	Number of patients eligible	Number of patients screened	% of eligible total tested	Number of patients eligible	Number of patients screened	% of eligible total tested
Total	**31,738**	543	1.7%	**58,512**	11,386	19.5%
Ethnicity						
Black	3,142	112	3.6%	6,866	545	7.9%
Bangladeshi	3,289	61	1.9%	3,357	905	27.0%
Indian	4,269	25	0.6%	5,499	1,148	20.9%
Pakistani	8,771	38	0.4%	19,001	6,814	35.9%
Other Asian	2,857	55	1.9%	4,790	350	7.3%
Eastern Caucasian	1,309	9	0.7%	3,126	406	13.0%
Other	8,101	243	3.0%	15,873	1,218	7.7%
Gender						
Female	16,549	304	1.8%	30,187	6,537	21.7%
Male	15,189	239	1.6%	28,324	4,848	17.1%
Missing	0	0	0.0%	1	1	100.0%
Age group						
18-19	882	6	0.7%	1,619	223	13.8%
20-29	9,523	180	1.9%	16,816	2,029	12.1%
30-39	10,023	185	1.9%	17,680	2,899	16.4%
40-49	5,413	113	2.1%	10,457	2,606	24.9%
50-59	2,846	38	1.3%	5,967	1,703	28.5%
60-69	1,602	17	1.1%	3,133	1,130	36.1%
70-79	935	2	0.2%	1,841	579	31.5%
80-89	450	2	0.4%	896	206	23.0%
90-99	60	0	0.0%	99	11	11.1%
100 and over	4	0	0.0%	4	0	0.0%

Table 14b Screening for viral hepatitis by ethnicity, gender and age in patients registered with the practice

	Standard screening (number of practices = 8)			Interventional screening (number of practices = 50)		
	Number of patients eligible	Number of patients screened	%	Number of patients eligible	Number of patients screened	%
Total	**26,046**	**271**	**1.0%**	**51,773**	**10,524**	**20.3%**
Ethnicity						
Black	2,619	67	2.6%	6,450	537	8.3%
Bangladeshi	2,837	47	1.7%	3,148	821	26.1%
Indian	3,506	13	0.4%	4,943	1,024	20.7%
Pakistani	7,874	24	0.3%	17,697	6,414	36.2%
Other Asian	2,376	28	1.2%	3,909	324	8.3%
Eastern Caucasian	965	1	0.1%	2,431	306	12.6%
Other	5,869	91	1.6%	13,195	1,098	8.3%
Gender						
Female	13,351	142	1.1%	26,548	6,059	22.8%
Male	12,695	129	1.0%	25,224	4,464	17.7%
Missing	-	-	-	1	1	100.0%
Age group						
18-19	882	6	0.7%	1,619	223	13.8%
20-29	7,107	56	0.8%	13,932	1,765	12.7%
30-39	8,035	94	1.2%	15,382	2,631	17.1%
40-49	4,681	66	1.4%	9,614	2,451	25.5%
50-59	2,550	30	1.2%	5,561	1,606	28.9%
60-69	1,472	16	1.1%	2,941	1,082	36.8%
70-79	865	1	0.1%	1,764	558	31.6%
80-89	397	2	0.5%	862	197	22.9%
90-99	54	0	0.0%	94	11	11.7%
100 and over	3	0	0.0%	4	0	0.0%

Table 14c Screening for viral hepatitis by ethnicity, gender and age in patients registering with practices throughout the study period

	Standard screening			Interventional screening		
	Number of patients eligible	Number of patients screened	%	Number of patients eligible	Number of patients screened	%
Total	**5,692**	272	4.8%	**6,739**	862	12.8%
Ethnicity						
Black	523	45	8.6%	416	8	1.9%
Bangladeshi	452	14	3.1%	209	84	40.2%
Indian	763	12	1.6%	556	124	22.3%
Pakistani	897	14	1.6%	1,304	400	30.7%
Other Asian	481	27	5.6%	881	26	3.0%
Eastern Caucasian	344	8	2.3%	695	100	14.4%
Other	2,232	152	6.8%	2,678	120	4.5%
Gender						
Female	3,198	162	5.1%	3,639	478	13.1%
Male	2,494	110	4.4%	3,100	384	12.4%
Missing	-	-	-	-	-	-
Age group						
18-19	-	-	-	-	-	-
20-29	2,416	124	5.1%	2,884	264	9.2%
30-39	1,988	91	4.6%	2,298	268	11.7%
40-49	732	47	6.4%	843	155	18.4%
50-59	296	8	2.7%	406	97	23.9%
60-69	130	1	0.8%	192	48	25.0%
70-79	70	1	1.4%	77	21	27.3%
80-89	53	0	0.0%	34	9	26.5%
90-99	6	0	0.0%	5	0	0.0%
100 and over	1	0	0.0%	0	0	0.0%

In patients registered with the practice at the start of the study there was a marked increase in the proportion of older patients (>40 years old) who attended for screening – attendance was 14.9% in patients aged less than 39 but 28% in older patients. The difference was also present in patients newly registering with practices during the study period. (11.4% in young patients cf 24.6% in older patients).

We compared screening rates in patients in intervention and control practices and there was a significant increase in incidence rate ratios for all participants (IRR = 3.7) as well as participants present at the start of the study (IRR = 5.2) (Table 15).

The difference in screening uptake between control and intervention groups was more marked in patients initially registered with the practice than new registrants; of the patients who were initially registered, 271 (1·0%) of 26 406 patients in the control practices were tested compared with 10 524 (20·3%) of 51 773 patients in the intervention practices (IRR 5·20, 1·89–14·34; p=0·001).

However, of newly registered patients, 272 (4·8%) of 5692 patients in control practices were tested compared with 862 (12·8%) of 6739 patients in intervention practices (1·52, 0·27–8·45; p=0·63).

Table 15: Incidence rate ratios for interventional versus standard screening for all participants and those registered at the start of the study

	Type of screening (number of practices)	**Numbers screened**		**Incidence rate ratio* [95% confidence interval]**	**p – value**
		Number	**%**		
All participants	Standard (8) Interventional (50)	543 / 31,738 11,386 / 58,512	1.7% 19.5%	3.697 [1.301 to 10.507]	0.014
Participants present at start of study	Standard (8) Interventional (50)	271 / 26,046 10,524 / 51,773	1.0% 20.3%	5.201 [1.887 to 14.34]	0.001

*adjusted for site and number of eligible patients

*adjusted for site and number of eligible patients

**Intracluster Correlation Coefficients, all participants = 0.028 (95% CI: 0.018 to 0.039)

**Intracluster Correlation Coefficients, participants present at start of study = 0.029 (95% CI: 0.018 to 0.039)

*** Screening rates were modelled using Poisson regression models. Dependent variable is number of patients screened in each GP practice. The number of eligible patients included as the exposure and practice as a random effect. The stratification factor - area and minimisation factor - number of eligible patients included as covariates in the model.

Table 16: Screening rates in new registrants *(as a % of new registrants deemed eligible for screening)*

Type of screening	Numbers screened		Tested positive	
	Number	%	Number	%
Standard screening *(number of practices = 8)*	272 / 5,692	4.8%	7 / 5,692	0.1%
Interventional screening *(number of practices = 15)*	862 / 6,739	12.8%	22 / 6,739	0.3%

*New registrants are persons registering with the practice after the trial initiation date and has not left the practice up until the date practice was closed for screening.

To examine the impact of a bespoke letter we compared screening rates in all patients who received the standard invitation letter. Table 17 details the analysis. There was no significant difference in screening rates with the two different letters.

Table 17: Testing outcomes after standard invitation vs enhanced invitation

Type of invitation	Numbers screened within 31 days of an invitation been sent		Incidence rate ratio* [95% confidence interval]	p - value
	Number	%		
Standard invitation *(number of practices = 18)*	720 / 15,844	4.5%		
Enhanced invitation *(number of practices = 32)*	1,032 / 28,095	3.7%	0.703 [0.378 to 1.306]	0.265

Prevalence of chronic viral hepatitis in patients who were screened.

The prevalence of chronic viral hepatitis in patients who were screened for infection is shown in Table 18. The prevalence in those originally registered with the practice and those who registered during the study is shown in Tables 12 and 13 respectively.

Table 18a Prevalence of infection in all participants screened

	Number of patients tested	Total tested positive		HBsAg + ve		HCV antibody + ve		HCV RNA + ve	
		Number	% of numbers tested	Number	% of number tested	Number	% of number tested	Number	% of number tested
Total	11,929	237	2.0	127	1.06	111	0.93	36	0.3%
Ethnicity									
Black	657	11	1.7	9	1.37	2	0.30	0	0.00
Bangladeshi	966	13	1.3	10	1.04	3	0.31	0	0.00
Indian	1,173	11	0.9	7	0.60	4	0.34	2	0.17
Pakistani	6,852	142	2.1	53	0.77	89	1.30	32	0.47
Other Asian	405	12	3.0	11	2.72	1	0.25	0	0.00
Eastern Caucasian	415	11	2.7	8	1.93	4	0.96	2	0.48
Other	1,461	37	2.5	29	1.98	8	0.55	0	0.00
Gender									
Female	6,841	104	1.5	41	0.60	63	0.92	20	0.29
Male	5,087	133	2.6	86	1.69	48	0.94	16	0.31
Missing	1								
Age group									
18-19	229	0	0.0	0	0.00	0	0.00	0	0.00
20-29	2,209	26	1.2	18	0.81	8	0.36	5	0.23
30-39	3,084	69	2.2	34	1.10	35	1.13	16	0.52
40-49	2,719	66	2.4	32	1.18	34	1.25	7	0.26
50-59	1,741	39	2.2	20	1.15	19	1.09	5	0.29
60-69	1,147	24	2.1	17	1.48	8	0.70	1	0.09
70-79	581	10	1.7	5	0.86	5	0.86	1	0.17
80-89	208	3	1.4	1	0.48	2	0.96	1	0.48
90-99	11	0	0.0	0	0.00	0	0.00	0	0.00
100 and over	0	0	0.0	0	0.00	0	0.00	0	0.00

The prevalence of infection was slightly increased in those older than 40 years of age – prevalence in those <39 years old was 1.95% compared to 2.06% in older patients.

Table 18b Prevalence of infection in patients registered with study practices at the start of trial

	Standard screening							Interventional screening							
		Total tested positive		HBsAg + ve		HCV antibody + ve		No. screened	Total tested positive		HBsAg + ve		HCV antibody + ve		HCV RNA + ve	
	No. screened	No.	% of screened	No	% of total positive	No	% of total positive		No	% of screened	No	% of total positive	No	% of positive	No	% of HCV +ve
Total	271	10	3.7%	7	70.0%	3	30.0%	10,524	19	1.9%	10	51.0%	98	49.5%	34	34.7%
Ethnicity																
Black	67	3	4.5%	2	66.7%	1	33.3%	537	8	1.5%	7	87.5%	1	12.5%	0	0.0%
Bangladeshi	47	2	4.3%	2	100.0%	0	0.0%	821	11	1.3%	8	72.7%	3	27.3%	0	0.0%
Indian	13	0	0.0%	0	0.0%	0	0.0%	1,024	9	0.9%	5	55.6%	4	44.4%	2	50.0%
Pakistani	24	2	8.3%	0	0.0%	2	100.0%	6,414	12	2.0%	48	37.5%	80	62.5%	30	37.5%
Other Asian	28	0	0.0%	0	0.0%	0	0.0%	324	8	2.5%	8	100.0%	0	0.0%	0	0.0%
Eastern Caucasian	1	1	100.0%	1	100.0%	0	0.0%	306	8	2.6%	5	62.5%	4	50.0%	2	50.0%
Other	91	2	2.2%	2	100.0%	0	0.0%	1,098	26	2.4%	20	76.9%	6	23.1%	0	0.0%
Gender																
Female	142	5	3.5%	2	40.0%	3	60.0%	6,059	85	1.4%	32	37.6%	53	62.4%	20	37.7%
Male	129	5	3.9%	5	100.0%	0	0.0%	4,464	11	2.5%	69	61.1%	45	39.8%	14	31.1%
Missing	0	0	0.0%	0	0.0%	0	0.0%	1	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Age group																
18-19	6	0	0.0%	0	0.0%	0	0.0%	223	0	0.0%	0	0.0%	0	0.0%	0	0.0%
20-29	56	2	3.6%	2	100.0%	0	0.0%	1,765	15	0.9%	10	66.7%	5	33.3%	4	80.0%
30-39	94	4	4.3%	4	100.0%	0	0.0%	2,631	55	2.1%	22	40.0%	33	60.0%	15	45.5%
40-49	66	2	3.0%	0	0.0%	2	100.0%	2,451	61	2.5%	32	52.5%	29	47.5%	7	24.1%
50-59	30	2	6.7%	1	50.0%	1	50.0%	1,606	34	2.1%	17	50.0%	17	50.0%	5	29.4%
60-69	16	0	0.0%	0	0.0%	0	0.0%	1,082	22	2.0%	15	68.2%	8	36.4%	1	12.5%
70-79	1	0	0.0%	0	0.0%	0	0.0%	558	8	1.4%	4	50.0%	4	50.0%	1	25.0%
80-89	2	0	0.0%	0	0.0%	0	0.0%	197	3	1.5%	1	33.3%	2	66.7%	1	50.0%
90 and over	0	0	0.0%	0	0.0%	0	0.0%	11	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Table 18c Prevalence of infection in patients screened who joined the study during the study period

	Standard screening							Interventional screening								
	Number of patients screened	Total tested positive		HBsAg + ve		HCV antibody + ve		No. of patients screened	Total tested positive		HBsAg + ve		HCV antibody + ve		HCV RNA + ve	
		No.	% of screened	No.	% of screened	No	% of screened		No.	% of screened	No.	% of positive	No.	% of positive	No.	% of HCV +ve
Total	272	7	2.6%	5	1.84%	2	0.74%	862	22	2.60%	1	1.62%	8	0.93%	2	0.23%
Ethnicity																
Black	45	0	0.0%	0	0.0%	0	0.0%	8	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Bangladeshi	14	0	0.0%	0	0.0%	0	0.0%	84	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Indian	12	0	0.0%	0	0.0%	0	0.0%	124	2	1.60%	2	1.61%	0	0.0%	0	0.0%
Pakistani	14	2	14.3%	2	14.29%	0	0.0%	400	10	2.50%	3	0.75%	7	1.75%	2	0.50%
Other Asian	27	2	7.4%	1	3.70%	1	3.70%	26	2	7.70%	2	7.69%	0	0.0%	0	0.0%
Eastern	8	0	0.0%	0	0.0%	0	0.0%	100	2	2.00%	2	2.00%	0	0.0%	0	0.0%
Other	152	3	2.0%	2	1.32%	1	0.66%	120	6	5.00%	5	4.17%	1	0.83%	0	0.0%
Gender																
Female	162	4	2.5%	2	1.23%	2	1.23%	478	10	2.10%	5	1.05%	5	1.05%	0	0.0%
Male	110	3	2.7%	3	2.73%	0	0.0%	384	12	3.10%	9	2.34%	3	0.78%	2	0.52%
Age group																
18-19	0	0	0.0%	0	0.0%	0	0.0%	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%
20-29	124	2	1.6%	1	0.81%	1	0.81%	264	7	2.70%	5	1.89%	2	0.76%	1	0.38%
30-39	91	5	5.5%	4	4.40%	1	1.10%	268	5	1.90%	4	1.49%	1	0.37%	1	0.37%
40-49	47	0	0.0%	0	0.0%	0	0.0%	155	3	1.90%	0	0.0%	3	1.94%	0	0.0%
50-59	8	0	0.0%	0	0.0%	0	0.0%	97	3	3.10%	2	2.06%	1	1.03%	0	0.0%
60-69	1	0	0.0%	0	0.0%	0	0.0%	48	2	4.20%	2	4.17%	0	0.0%	0	0.0%
70-79	1	0	0.0%	0	0.0%	0	0.0%	21	2	9.50%	1	4.76%	1	4.76%	0	0.0%
80-89	0	0	0.0%	0	0.0%	0	0.0%	9	0	0.0%	0	0.0%	0	0.0%	0	0.0%
90-99	0	0	0.0%	0	0.0%	0	0.0%	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%
100 and over	0	0	0.0%	0	0.0%	0	0.0%	0	0	0.0%	0	0.0%	0	0.0%	0	0.0%

3.3 Engagement in Care Outcomes

Overall (including patients in the control group), of 11 929 patients who were tested, 237 (2·0%) patients, including one patient who tested positive for HBsAg and for HCV, tested positive for viral hepatitis (table 18a): 111 (0·9%) patients had antibodies against HCV, of whom 36 (32·4%; 0·3% of those tested) were viraemic, and 127 (1·1%) patients tested positive for HBsAg.

A higher proportion of newly registered patients tested positive for viral hepatitis than registered patients: 29 (2·6%) of 1134 new patients compared with 271 (2·5%) of 10 795 registered patients. In post-hoc analyses, we noted a greater proportion of positive tests for viral hepatitis in patients screened in control practices, in which 17 (3·1%) of 543 patients were positive versus 220 (1·9%) of 11 386 patients in the intervention practices, including one patient with a co-infection (i.e., 221 diagnoses in 220 patients).

The 220 (0·4%) of 58 512 patients who were eligible for testing and tested positive from intervention practices (1·9% of 11 386 patients tested) were eligible to enrol in the second embedded trial of community versus hospital care; the groups were well matched. Figure 13 outlines the engagement outcomes for these 220 patients.

129 (58·6%) of the 220 patients with infections were randomly assigned to receive community care and 91 (41·4%) patients were assigned to receive standard, hospital-based care. Of the 220 patients included, nine were already receiving hospital care (which was not known to the general practices) and 21 (9·5%) did not attend for a diagnostic assessment.

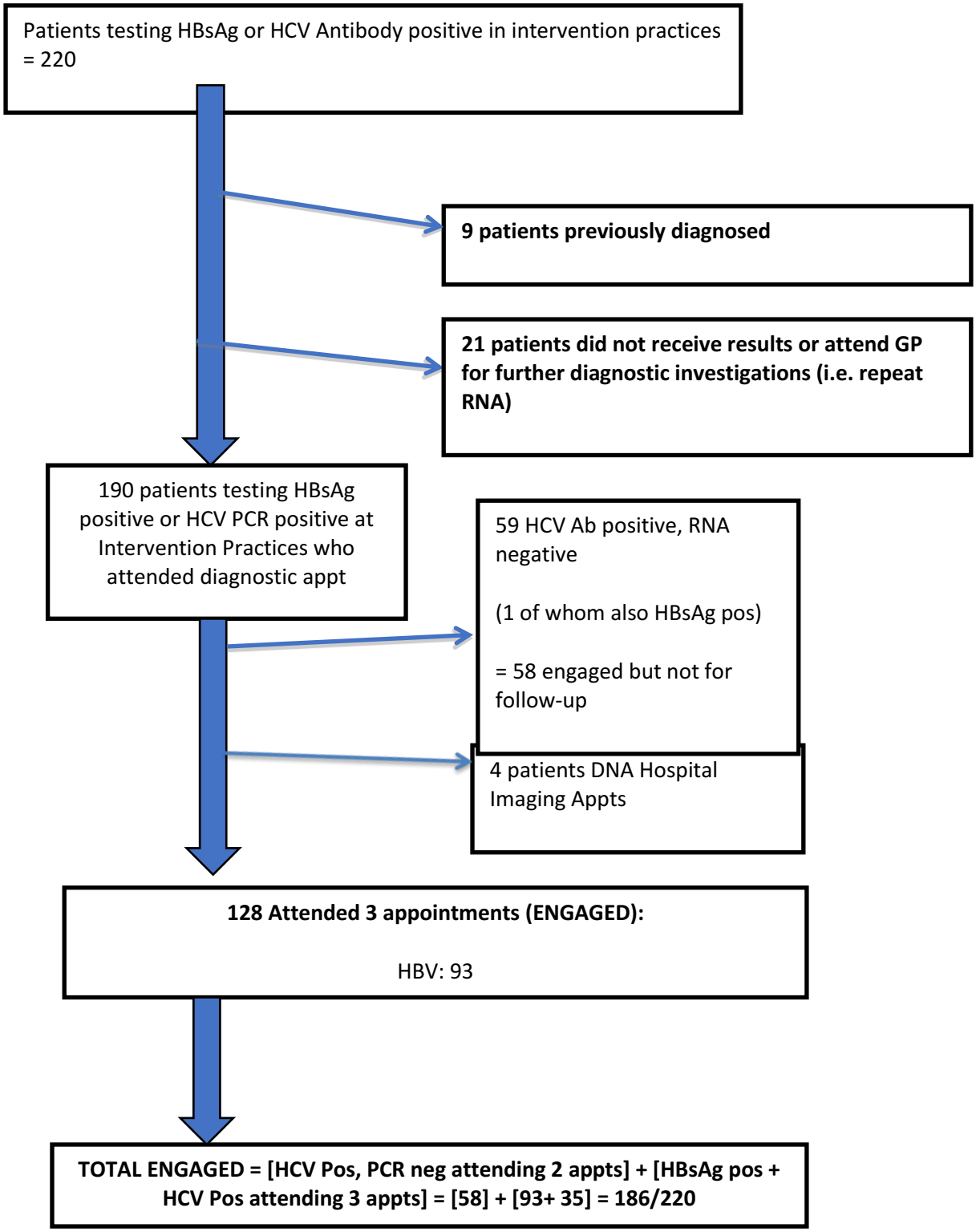
Of the 190 patients who attended for a diagnostic assessment, one (0·5%) patient died before completion of the tests, and nine (4·7%) patients did not attend for all the tests. 52 patients who were positive for HCV antibodies were not viraemic.

128 (58·1%) of 220 patients engaged in diagnostic and prognostic assessment (93 patients with HBV and 35 patients with HCV).

Engagement with the diagnostic and prognostic assessment did not differ significantly between the groups; in an intention-to treat analysis, 80 (87·9%) of 91 patients receiving standard care engaged with diagnostic and prognostic assessment compared with 105 (81·4%) of 129 patients receiving community care (94 patients with HCV and 89 patients with HBV; IRR 0·76, 95% CI 0·2–2·5; p=0·65).

Patient engagement by protocol is outlined in Figure 13. Disease staging and treatment outcomes for these patients is further analysed and discussed in Chapter 4.

Figure 13: Patient engagement by protocol



In a per-protocol analysis, we found that, of the 13 patients with HBV who were randomly assigned to receive standard care, 12 (92%) patients complied with recommended management (observation) versus 22 (88%) of 25 patients randomly assigned to community care, in which one patient required therapy (and adhered to treatment). In the 55 patients who did not consent to be randomly assigned and were treated in the hospital setting, 49 (89%) patients complied with the recommended regimen.

Of the 36 patients with HCV who were viraemic, 35 patients engaged with follow up: eight patients were treated in the community care group and all (100%) were adherent. 27 patients were treated in standard hospital settings (four patients in the trial group allocated to this setting and 23 by default), and all (100%) were adherent.

Cost-effectiveness analysis was performed by the Healthcare Modelling team at Exeter University. In the base-case, the intervention was cost-effective at willingness to pay (WTP) thresholds in excess of £8540 per QALY. Treatment with pure direct-acting antiviral regimens for HCV made the joint intervention (screening and treatment) cost-effective at WTP thresholds between £6935 and £18 185 per QALY dependent on pricing and the regimen or treatment duration applied.

Treatment of people older than 40 years (mean age 50 years) was cost-effective at WTP thresholds in excess of £15 696.

Screening based on ethnic background was cost-effective for Pakistani ethnicity at WTP thresholds in excess of £9523 per QALY. The intervention was unlikely to be cost-effective for cohorts with a mean age older than 56 years. Results from the probabilistic sensitivity analysis indicated that the intervention is likely to be cost-effective in the most scenarios, with a mean incremental cost-effectiveness ratio of £5292. This result is lower than the deterministic mean, in part because the probabilistic analysis adjusts for the small numbers tested in some of the larger GP practices.

This issue appears to have predominantly affected practices where HBV was the more prevalent infection.

During the treatment phase, one patient who was treated with interferon developed thyroiditis, but no other trial-related harms were noted during the study. 515 (7·5%) of 6854 eligible patients in Oxford were tested for viral hepatitis, and a similar trend was observed to that of the main trial: older patients from the Indian subcontinent were most likely to attend screening. In Oxford, seven (1·4%) of 515 patients who were tested had positive tests, all of whom were infected with HBV.

3.4 Discussion

Current NICE guidelines recommend testing individuals at high risk of chronic viral hepatitis in the primary care setting. This high-risk group includes immigrants. Therefore, the HepFREE trial was designed to address the issues around testing immigrants in primary care.

In control practices testing of patients registered with the practice was low (1%) but testing in new registrants was much greater (4.8%). By contrast testing in intervention practices that were incentivised to participate was much greater with 20% of registered patients undergoing testing whilst only 12.8% of new registrants were tested.

Testing rates differed by ethnic group with people originally from Pakistan more likely to participate in screening. There was also an important difference in uptake by age – older people (>40 years) were more likely to attend than younger people and the prevalence of viral hepatitis was slightly greater in these patients. These data suggest that screening may be more productive if it is focussed on older individuals.

The overall prevalence of viral hepatitis was 2% but most patients with HCV had cleared virus. This may have been due to higher rates of viral clearance in elderly, healthy migrant patients compared to the indigenous, often younger, drug using population or whether this is an artefact of our selection criteria with people attending GP surgeries being more likely to have cleared virus, perhaps because their liver function tests are normal and therefore they have not been previously tested. However, the overall HCV viraemia of 0.3% was shown to be sufficient to justify screening using standard cost effectiveness calculations (not presented here).
Generational risk was not specifically measured, but we can extrapolate that individuals born in the UK were at least 2nd generation migrants. Of those testing positive (see chapter 4 Results) 4/128 (3.1%) were UK-born. This strongly suggests that high prevalence country of birth is a better indicator of viral hepatitis risk than ethnicity.

The WHO goals of eliminating viral hepatitis by 2030 will require increased testing and treatment of high-risk communities. HepFREE shows that in areas of high migrant density testing for viral hepatitis in primary care is an effective strategy that leads to high rates of detection of infection that is associated with excellent therapeutic adherence. This is particularly marked for people over the age of 40.

4. Results: Disease Staging for Patients Testing Positive for Viral Hepatitis

4.1 Introduction

In this chapter I report on the disease staging of patients who tested positive for HBsAg or HCV Ab in the HepFREE trial. Staging of viral hepatitis liver disease is a key predictor of prognosis, as well as informing treatment and on-going management for patients with chronic HBV and HCV infection. Understanding the disease staging of patients who enrol in screening clarifies the need for screening for a condition and the health benefits of screening in further cost-effectiveness analysis.

Data collection, collation and analysis were performed by me.

4.2 Numbers of Positive Patients

From the total 11,929 patient screened for HBsAg and HCV Ab in both control and intervention practices, 237 (2.0%) patients tested positive for HBsAg or HCV Ab (including one patient who tested positive for both). (See Table 18a, chapter 3).

110 (0·9%) patients had antibodies against HCV, of whom 35 (31.8%; 0·3% of those tested) were viraemic, and 127 (1·1%) patients tested positive for HBsAg.

In both control and intervention practices, a higher proportion of newly registered patients tested positive for viral hepatitis than registered patients: 29 (2·6%) of 1134 new patients compared with 271 (2·5%) of 10,795 registered patients. (See Tables 18b and 18c, chapter 3).

There was a greater proportion of positive tests for viral hepatitis in patients screened in control practices, in which 17 (3·1%) of 543 patients were positive versus 220 (1·9%) of 11,386 patients in the intervention practices, including one patient with a co-infection (i.e., 221 diagnoses in 220 patients).

We did not have ethical approval to collect follow-up data from patients diagnosed positive in the control arm of the HepFREE Screening trial, and therefore those 17 patients are not included in this disease staging analysis.

220 (0·4%) of 58 512 tested patients from intervention practices tested positive (1·9% of 11,386 patients tested) and were followed up regarding disease staging, and treatment and management. In this chapter I present my exploratory analysis of the viral hepatitis disease stage for this population.

4.3 Positive Results in the Intervention Arm

As per the HepFREE trial protocol, if patients were already known to be HBsAg positive, or HCV Ab positive, they were not eligible for invitation to screening. However, 9 patients of the 220 who tested positive were known to be HBsAg or HCV positive, and engaged appropriately in care. This had not been recorded on their GP records and therefore they were not excluded by the HepFREE eligibility search. Although these patients were not eligible for further follow-up, the GP records were amended so that their medical history was correctly coded.

One patient tested positive for viral hepatitis but withdrew consent to the HepFREE trial prior to being referred to secondary care. Their data has not been collected for further analysis. Therefore, 210 of the patients who tested positive for HBsAg or HCV Ab (or both) in intervention practices were eligible for follow-up analysis.

4.3.1 GP Results Attendance

As per the HepFREE protocol, all patients testing for viral hepatitis in the HepFREE trial were to be informed by their GP practice of the outcome of the screening test.

8 patients who tested positive for viral hepatitis were not informed by their GP of the result, and therefore were not referred to Secondary Care for follow-up. I had access to the virology laboratory results and an anonymous linking code for these patients, but no demographics data.

8 patients who were not informed of their results had the following test results:

- HBsAg Positive = 3 patients
- HCV Positive, RNA negative = 3 patients
- HCV Positive, RNA not done = 1 patient
- HCV Positive, RNA Positive = 1 patient

202 Patients required a diagnostic appointment after testing positive with newly confirmed viral hepatitis HBsAg positive or HCV antibody positive in intervention practices.

4.3.2 Diagnostic Appointments

Diagnostic Appointments fell into the one of the following four categories:

1. GP appointment to repeat HCV RNA test after a previous HCV Ab, RNA negative result.
2. Secondary Care appointment to repeat HCV RNA test after a previous HCV Ab, RNA negative result.

3. Secondary Care appointment after a previous HCV Ab, RNA positive result to assess demographics, medical history and arrange serology testing for FBC, Urea & Electrolytes, LFTs, HCV genotype and HCV viral load, and to arrange Fibroscan® and ultrasound imaging appointments.
4. Secondary Care appointment after a previous HBsAg positive result to assess demographics, medical history and arrange serology testing for FBC, Urea & Electrolytes, LFTs, HBeAg and HBV viral load, and to arrange Fibroscan® and ultrasound imaging appointments.

12 patients Did Not Attend Secondary Care Diagnostic or repeat GP testing (if HCV RNA negative or equivocal x 1 sample).

- HBsAg Positive = 7 patients
- HCV Positive, RNA Positive & Deceased = 1 patient*
- HCV Positive, RNA Positive = 2 patients
- HCV Positive, RNA Negative (on 1 sample) = 1 patient
- HCV Positive RNA unknown = 1 patient

*The deceased patient died from causes unrelated to their HCV infection (prostate cancer) and were tested during their palliative care phase.

9 of the patients were from Bradford, 1 from East London and 2 from South London. 8 were male and 4 female, with an age range of 27-61 years. 5 patients were from Pakistan and 4 from Eastern Europe, the other 3 patients did not have country of birth recorded on their GP records.

4.3.2.1 Patients who Attended Diagnostic Appointments

190 Patients tested HBsAg positive or HCV PCR positive at Intervention Practices and attended Diagnostic Appointments at Primary of Secondary Care

131 of these patients were HBsAg positive or HCV Ab + RNA pos and attended their diagnostic appointment in Secondary Care.

58 patients were HCV Ab Pos + RNA neg (on two samples) and attended their diagnostic appointment in either primary or secondary care. These 58 patients were regarded as engaged although they did not require further disease staging.

1 patient was HBsAg positive and also HCV Ab pos and RNA neg (on two samples). This patient attended their diagnostic appointment and was followed up for disease staging of Hepatitis B infection.

4.3.2.2 Patients Not Attending Imaging Appointments

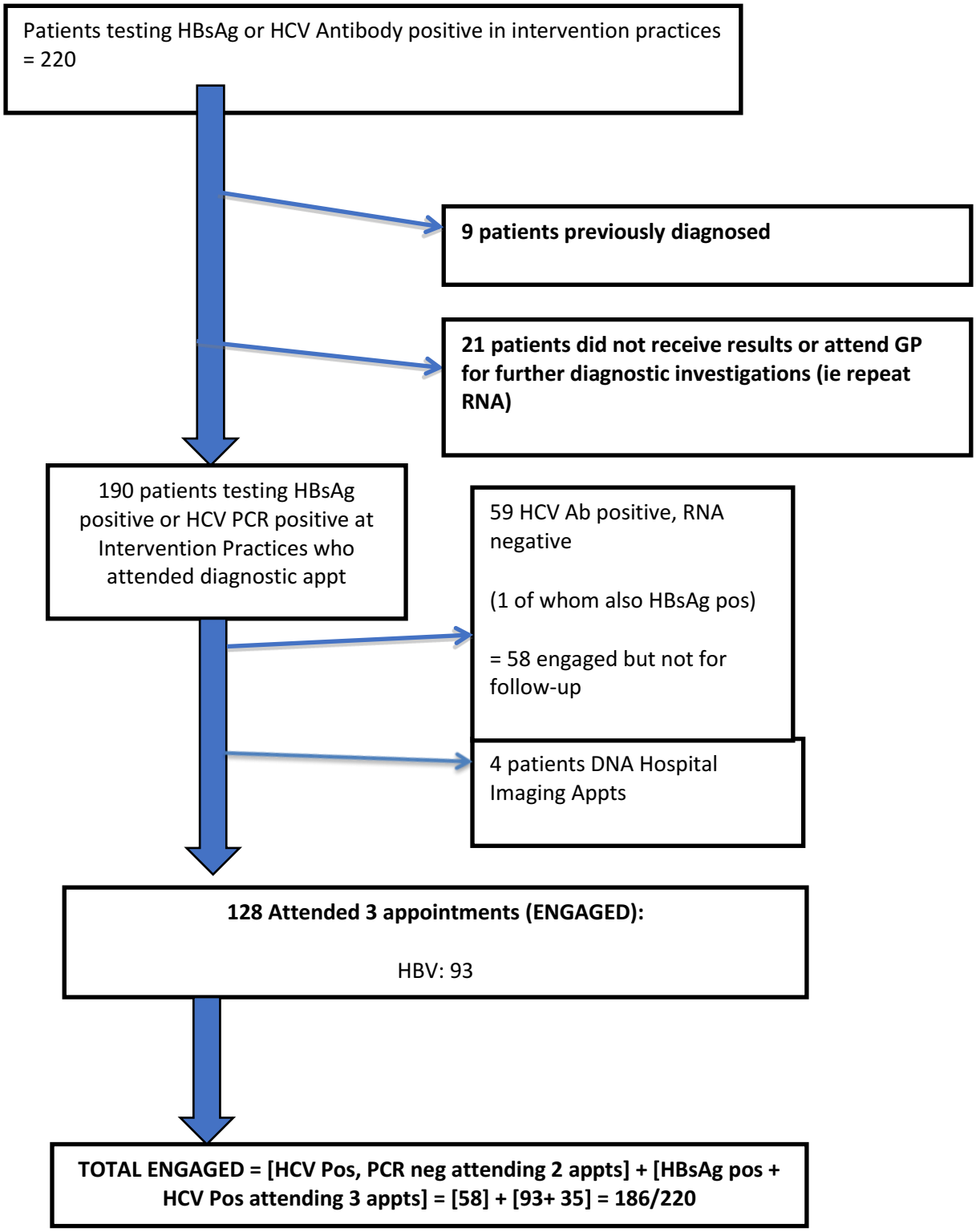
Of the 132 attending the diagnostic appointment, 4 did not attend their Fibroscan® and/or ultrasound liver imaging appointments for disease staging.

These 4 patients broke down as follows: 2 male, 2 female, 2 from Bradford and 2 from London. All 4 patients had tested HBsAg positive. Age range was 32-72. None of the patients had tested HBeAg positive or HDV positive on their baseline serology tests.

4.3.2.3 Patients who Attended Diagnostic and Imaging Appointments

A total of 186 (88.6%) of 210 patients testing positive for viral hepatitis in the HepFREE Screening trial who were eligible for follow-up engaged in diagnostic and prognostic assessment as per protocol. 93 patients were diagnosed with HBV, 58 with non-viraemic HCV and 35 patients with viraemic HCV. Figure 13 showing engagement for these patients was included in Chapter 3 but is repeated here for ease of reference.

Figure 13: Patient engagement by protocol



4.4 Demographics of Patients Testing HBsAg Positive

93 (95·9%) of 97 patients with HBsAg completed a diagnostic and imaging assessment:

65 patients were male, 28 female.

- two (2·1%) patients had a coinfection with hepatitis D virus
- five (5·4%) patients tested positive for HBeAg (a marker of HBV replication)
- eight (8.6%) patients had severe fibrosis or cirrhosis on liver biopsy.

Table 19: Demographic, Diagnostic and Imaging outcomes of HBsAg positive Patients

Page 1	Gender	Age (years)	Location	Country of Birth	HBeAg Status	HDV Infection	HBV DNA (copies/ mL) at baseline	ALT (IU/mL) at baseline	US Report	Transient Elastography Score (kPa)	Treatment Plan	Outcome
1	Female	56	Bradford	Pakistan	Negative	Negative	1.0×10^3	21	No cirrhosis	4.1	Observe	
2	Male	N/A	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	7.5	Observe	
3	Male	34	Bradford	Bangladesh	Negative	Negative	2.8×10^2	44	No cirrhosis	5.8	Observe	
4	Male	33	Bradford	Bangladesh	Negative	Negative	1.1×10^3	36	No cirrhosis	7.8	Observe	
5	Male	N/A	Bradford	Afghanistan	Negative	Negative	------	------	No cirrhosis	7.3	Observe	
6	Male	35	Bradford	Gambia	Negative	Negative	4.7×10^2	32	No cirrhosis	8.7	Observe	
7	Male	36	Bradford	Pakistan	N/A	Negative	1.3×10^2	23	No cirrhosis	4.9	Observe	
8	Male	36	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	4.3	Interferon Treatment	Awaited
9	Male	41	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	3.8	NRTI (Tenofovir) Treatment	VL undetectable after 3 months
10	Male	64	Bradford	Africa	Negative	Negative	------	------	No cirrhosis	5.7	Observe	
11	Male	39	Bradford	Ghana	Negative	Negative	1.6×10^3	34	No cirrhosis	4.7	Observe	
12	Female	30	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	5.4	Observe	
13	Male	47	Bradford	Bangladesh	Negative	Negative	1.1×10^3	23	No cirrhosis	5.4	Observe	
14	Male	63	Bradford	Pakistan	Negative	Negative	1.3×10^2	24	No cirrhosis	6.8	Observe	
15	Male	61	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	4.4	Observe	

Page 2	Gender	Age (years)	Location	Country of Birth	HBeAg Status	HDV Infection	HBV DNA (copies/ mL) at baseline	ALT (IU/mL) at baseline	US Report	Transient Elastography Score (kPa)	Treatment Plan	Outcome
16	Male	N/A	Bradford	Pakistani British	Negative	Negative	83	20	No cirrhosis	5.3	Observe	
17	Male	48	Bradford	Pakistan	Negative	Negative	7.5×10^2	24	No cirrhosis	3.2	Observe	
18	Male	39	Bradford	Pakistan	Negative	Positive	71	79	No cirrhosis	9.4	Observe	
19	Male	41	Bradford	Pakistan	Negative	Negative	2.0×10^3	21	No cirrhosis	3.3	Observe	
20	Male	62	Bradford	Pakistan	Negative	Negative	7.2×10^2	22	No cirrhosis	4.5	Observe	
21	Male	60	Bradford	Pakistan	Negative	Negative	2.0×10^2	32	No cirrhosis	2.0	Observe	
22	Male	21	Bradford	Pakistan	Negative	Negative	1.6×10^3	32	No cirrhosis	5.6	Observe	
23	Female	54	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	4.1	Observe	
24	Female	59	Bradford	India	Negative	Negative	1.3×10^3	23	No cirrhosis	7.1	Observe	
25	Female	48	Bradford	Pakistan	Negative	Negative	6.3×10^2	23	No cirrhosis	5.0	Observe	
26	Male	48	Bradford	Pakistan	Negative	Negative	10.0×10^2	28	No cirrhosis	4.0	Observe	
27	Female	53	Bradford	Lithuania	Negative	Positive	3.2×10^2	23	No cirrhosis	5.9	Observe	
28	Female	61	Bradford	Pakistan	Negative	Negative	46	19	No cirrhosis	4.1	Observe	
29	Female	67	Bradford	Pakistan	Negative	Negative	1.2×10^3	23	No cirrhosis	8.9	Observe	
30	Male	31	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	4.9	Observe	
31	Male	40	Bradford	Pakistan	Negative	Negative	1.4×10^2	21	N/A	7.8	Observe	
32	Female	27	Bradford	Pakistan	Negative	Negative	3.4×10^3	20	No cirrhosis	5.6	Observe	
33	Male	48	Bradford	Poland	Negative	Negative	3.7×10^4	53	Cirrhosis	10	Interferon Treatment	IFN Stopped and switched to Tenofovir. Undetectable at 3 months
34	Male	30	Bradford	Latvia	Negative	Negative	------	------	No cirrhosis	6.3	Observe	
35	Female	32	Bradford	Pakistan	Negative	Negative	6.1×10^3	20	No cirrhosis	4.8	Observe	
36	Female	52	Bradford	India	Negative	Negative	<20	18	No cirrhosis	4.9	Observe	
37	Male	22	Bradford	Chinese British	Positive	Negative	4.9×10^2	32	No cirrhosis	4.7	Observe	

Page 3	Gender	Age (years)	Location	Country of Birth	HBeAg Status	HDV Infection	HBV DNA (copies/ mL) at baseline	ALT (IU/mL) at baseline	US Report	Transient Elastography Score (kPa)	Treatment Plan	Outcome
38	Male	25	Bradford	Chinese British	Negative	Negative	20	26	No cirrhosis	4.8	Observe	
39	Male	53	Bradford	India	Negative	Negative	------	------	No cirrhosis	3.9	Observe	
40	Female	21	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	4.8	Observe	
41	Male	63	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	3.3	Observe	
42	Female	60	Bradford	Latvia	Negative	Negative	------	------	No cirrhosis	10.1	Observe	
43	Male	28	Bradford	Pakistan	Negative	Negative	<20	54	No cirrhosis	4.0	Observe	
44	Male	58	Bradford	Pakistan	Negative	Negative	3.4×10^3	40	No cirrhosis	6.8	Interferon Treatment	Awaited
45	Female	43	Bradford	India	Negative	Negative	------	------	No cirrhosis	N/A	Observe	
46	Female	62	Bradford	Pakistan	Negative	Negative	<20	26	No cirrhosis	8.2	Observe	
47	Female	58	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	N/A	Entecavir Treatment	Awaited
48	Female	32	Bradford	Pakistan	Negative	Negative			Cirrhosis	19.6	Observe	
49	Male	42	Bradford	Pakistan	Negative	Negative	27	34	No cirrhosis	12.6	Observe	
50	Female	44	Bradford	Pakistan	Negative	Negative	<20	18	No cirrhosis	3.3	Tenofovir Treatment	Awaited
51	Female	45	Bradford	Pakistani British	Negative	Negative	2.9×10^2	19	No cirrhosis	5.3	Observe	
52	Male	22	Bradford	Pakistani British	Positive	Negative	1.7×10^8	92	No cirrhosis	4.6	Tenofovir Treatment	Awaited
53	Male	46	Bradford	Pakistan	Negative	Negative	1.1×10^3	27	No cirrhosis	4.1	Observe	
54	Female	44	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	4	Entecavir Treatment	Awaited
55	Male	55	Bradford	Pakistan	Negative	Negative	<20	62	No cirrhosis	11.4	Observe	
56	Male	42	Bradford	Pakistan	Negative	Negative	1.5×10^3	28	N/A	5.8	Observe	
57	Male	75	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	6.3	Observe	
58	Male	57	Bradford	Pakistan	Negative	Negative	5.4×10^2	21	Cirrhosis	6.4	Observe	
59	Female	45	Bradford	Pakistan	Negative	Negative	------	------	No cirrhosis	N/A	Entecavir Treatment	Awaited
60	Male	83	Bradford	Pakistan	Negative	Negative	<40	13	No cirrhosis	6.1	Observe	
61	Female	27	East London	Romania	Negative	Negative	521	16	No cirrhosis	4.2	Observe	
62	Male	20	East London	Romania	Negative	Negative	<100	20	No cirrhosis	5.5	Observe	

Page 4	Gender	Age (years)	Location	Country of Birth	HBeAg Status	HDV Infection	HBV DNA (copies/ mL) at baseline	ALT (IU/mL) at baseline	US Report	Transient Elastography Score (kPa)	Treatment Plan	Outcome
63	Male	75	East London	Nigeria	Negative	Negative	<20	28	No cirrhosis	10	Observe	
64	Male	29	East London	India	Negative	Negative	<100	22	No cirrhosis	4.3	Observe	
65	Male	39	East London	Bangladesh	Negative	Negative	1510	26	No cirrhosis	4.5	Observe	
66	Male	39	East London	India	Negative	Negative	1896	29	No cirrhosis	4.7	Observe	
67	Male	29	East London	Moldova	Positive	Negative	>500,000	42	No cirrhosis	9.1	Plan for NRTI (Tenofovir) Treatment	Lost to Follow-Up
68	Male	73	East London	Pakistan	Negative	Negative	482	19	No cirrhosis	3.7	Observe	
69	Male	44	East London	Somalia	Negative	Negative	<20	19	No cirrhosis	3.2	Observe	
70	Male	74	East London	Pakistan	Negative	Negative	133,140	39	No cirrhosis	8.1	Observe	
71	Male	62	East London	Pakistan	Negative	Negative	2814	22	No cirrhosis	5.6	Observe	
72	Male	34	East London	Bangladesh	Negative	Negative	4294	24	No cirrhosis	5.3	Observe	
73	Female	37	East London	Bangladesh	Negative	Negative	<100	16	No cirrhosis	3.8	Observe	
74	Male	57	East London	Pakistan	Negative	Negative	<100	22	No cirrhosis	5.2	Observe	
75	Male	41	South London	Ivory Coast	Negative	Negative	37,000	23	Cirrhosis	7.1	Observe	
76	Male	37	South London	Poland	Negative	Negative	1.05×10^3	38	No cirrhosis	6.1	Observe	
77	Male	71	South London	Vietnam	Negative	Negative	<20	20	No cirrhosis	6.8	Observe	
78	Male	39	South London	Sierra Leone	Negative	Negative	310	16	No cirrhosis	6.8	Observe	
79	Female	41	South London	Bulgaria	Negative	Negative	1.52×10^2	17	No cirrhosis	3.4	Observe	
80	Male	43	South London	Sierra Leone	Negative	Negative	3.75×10^1	20	No cirrhosis	4.5	Observe	
81	Female	40	South London	Sierra Leone	Negative	Negative	2.51×10^4	19	No cirrhosis	3.3	NRTI (Tenofovir) Treatment	Undetectable after 3 months
82	Male	48	South London	Ghana	Negative	Negative	1.13×10^3	27	No cirrhosis	4.5	Observe	
83	Female	63	South London	Sierra Leone	Negative	Negative	1.72×10^2	18	No cirrhosis	4.2	Observe	
84	Male	53	South London	Nigeria	Negative	Negative	<100	22	No cirrhosis	3.5	Observe	

Page 5	Gender	Age (years)	Location	Country of Birth	HBeAg Status	HDV Infection	HBV DNA (copies/ mL) at baseline	ALT (IU/mL) at baseline	US Report	Transient Elastography Score (kPa)	Treatment Plan	Outcome
85	Male	59	South London	Vietnam	Positive	Negative	1.8×10^6	29	No cirrhosis	3.7	Yes / No - seroconverted	
86	Male	49	South London	Ghana	Positive	Negative	1.39×10^6	28	No cirrhosis	8.2	NRTI (Tenofovir) Treatment	Undetectable after 3 months
87	Male	59	South London	Ghana	Negative	Negative	2.4×10^3	25	No cirrhosis	4.3	Observe	
88	Male	30	South London	Albania	Negative	Negative	6.0×10^2	22	No cirrhosis	5.4	Observe	
89	Female	46	South London	China	Negative	Negative	485	16	No cirrhosis	2.8	Observe	
90	Female	33	South London	Ghana	Negative	Negative	<1000	17	No cirrhosis	5.3	Observe	
91	Male	59	South London	Nigeria	Negative	Negative	6.44×10^1	26	No cirrhosis	5.2	Observe	
92	Male	41	South London	Ghana	Negative	Negative	3.12×10^3	28	No cirrhosis	5.5	Observe	
93	Male	47	South London	Nigeria	Negative	Negative	2.34×10^3	26	No cirrhosis	6.1	Observe	

NB where Country of Birth is UK, patients are eligible by their ethnicity (e.g. Chinese British, Pakistani British). Data on Viral Load and ALT was not recorded on OpenClinica for 19/93 patients as their data was collected prior to the platform including these parameters.

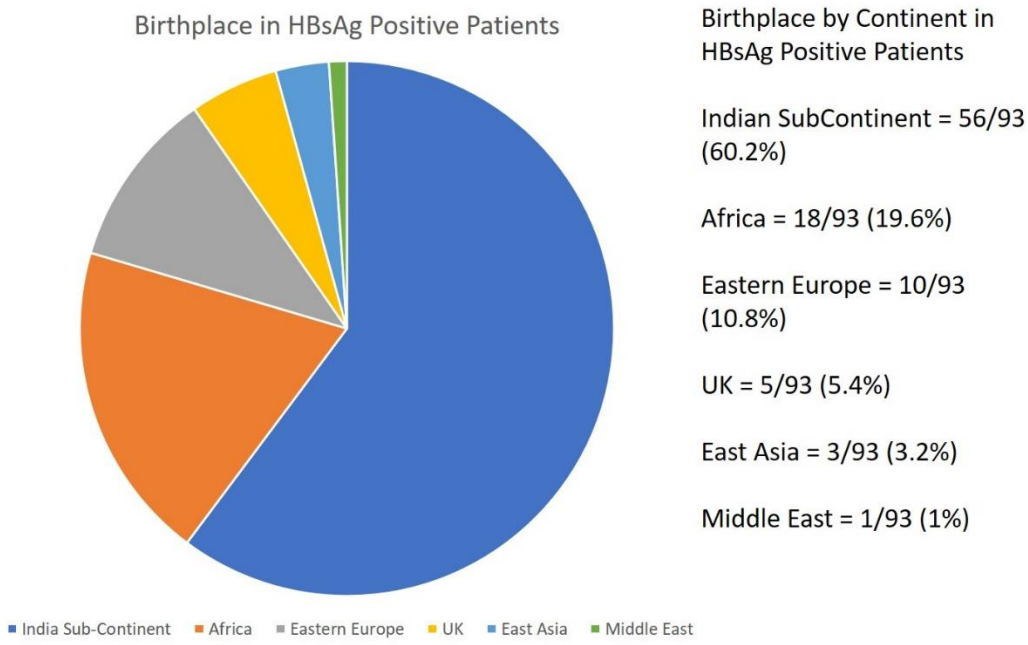


Figure 14a: Birthplace of HBsAg positive patients

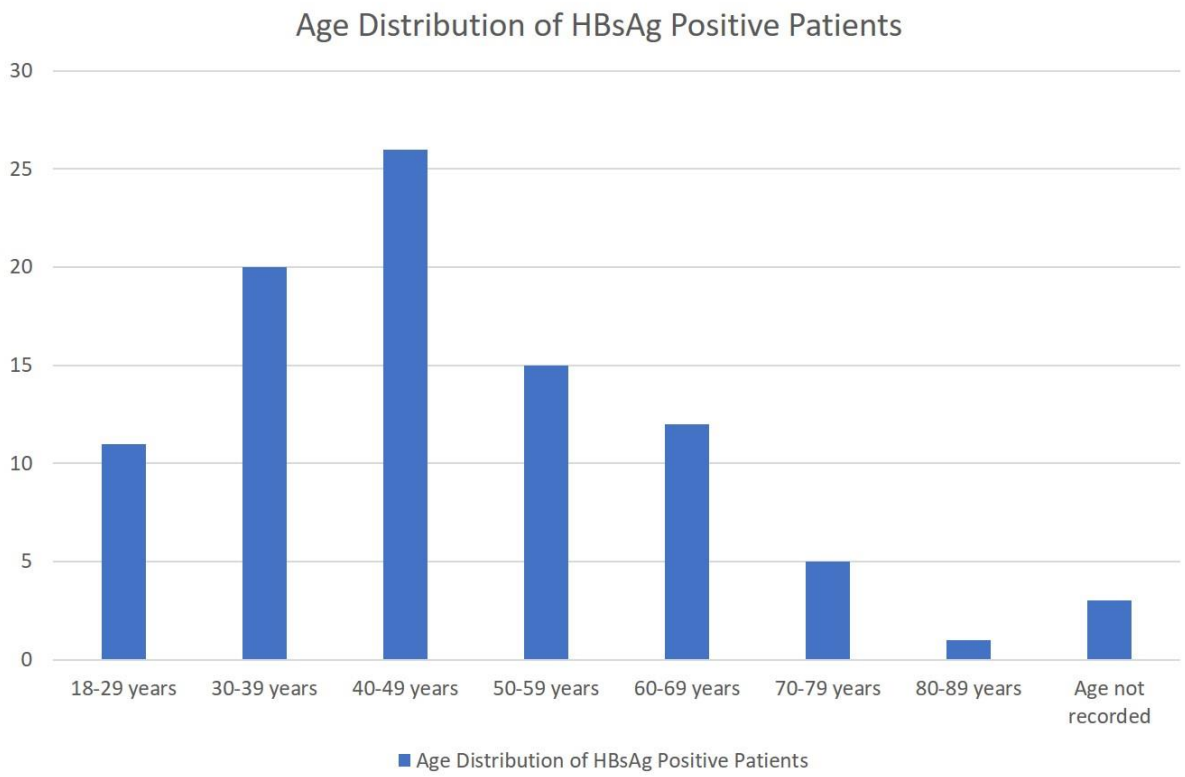


Figure 14b: Age Distribution of HBsAg positive patients

69.9% of patients testing HBsAg positive were male, with the majority of patients originally from the Indian Subcontinent (ISC = Pakistan, India, Bangladesh). This reflects the local demographics of the testing areas in Bradford and East London where in some GP practices up to 50% of the registered population were born in ISC, or born to parents from the ISC.

The majority of patients were aged <50 years (57/93, 61.3%) which suggests that testing in this age range in migrant populations will detect chronic HBsAg infection.

4.5 Disease Staging Assessment for Patients Testing HBsAg Positive

Of the 93 patients with HBsAg who completed diagnostic and imaging assessment:

- two (2·1%) patients had a coinfection with hepatitis D virus
- five (5·4%) patients tested positive for HBeAg (a marker of HBV replication)
- eight (8.6%) patients had severe fibrosis or cirrhosis on transient elastography or liver ultrasound.

4.5.1 Hepatitis Delta Virus coinfection

Two patients were co-infected with Hepatitis Delta Virus (HDV): 1 male and 1 female patient, both located in Bradford.

The patients were from Pakistan and Lithuania.

Ages were 39 and 53 years.

Both had no cirrhosis on US Liver.

Fibroscan® scores were 5.9KpA and 9.4KpA.

The management plan for both patients was for ongoing observation.

4.5.2 HBeAg positive patients

5 patients tested HBeAg positive (2 in Bradford, 2 in South East London and 1 in East London).

All patients were male.

None had cirrhosis on US Liver or on Fibroscan® (range of score 4.1kPa-9.2kPa)

Country of Birth was 1 x Chinese British, 1 x Pakistani British, 1 x Moldova, 1 x Vietnam, 1 x Ghana.

Age range was 22-59 years with the mode 22 years and the median 29 years.

Management plans for the 5 patients were:

1 patient to be treated with NRTIs: as age >30 years, VL >20,000 copies/mL and ALT >30 Units/L. This patient did not attend for their treatment follow-up appointments, and therefore was not started on treatment.

1 patient seroconverted to eAb positive during diagnostic and imaging investigations, and therefore was for observation (Age > 30, normal LFTs).

1 patient was offered treatment with NRTIs (Tenofovir): as age >30 years, HBV DNA >2000 copies/mL, ALT >30 Units/L on 2 tests. This patient continued to engage in therapy and achieved a reduction in viral load by more than 80% within 3 months of starting treatment.

For 2 patients the management plan was observation only. Both these patients were aged <30 years, had a viral load <2000 copies and normal LFTs.

4.5.3 HBsAg positive, HDV negative and HBeAg negative patients

86 patients without HDV co-infection or presence of eAg were assessed for chronic hepatitis B infection. 9 of these patients met the EASL criteria for treatment on the basis of ALT, HBV DNA viral load or presence of cirrhosis. Of these 9 patients, 4 were offered treatment for HBV infection. The other 82 patients were for ongoing observation.

My disease analysis of patients testing positive for HBsAg was performed to understand the progression of liver disease in patients identified in the HepFREE trial. In the trial, patients offered the screening test were not known to have abnormal liver function and therefore screening was performed in asymptomatic patients. My expectation was that a majority of patients would have normal liver function biochemistry and normal liver architecture. This was the case, however, the finding of severe liver fibrosis or cirrhosis in 8.6% of patients with hepatitis B indicates that a minority of patients in this population can develop significant disease without developing symptoms. The ongoing risk for these patients is considerable and there may be missed opportunities to offer treatment and observation if they are not identified as hepatitis B positive.

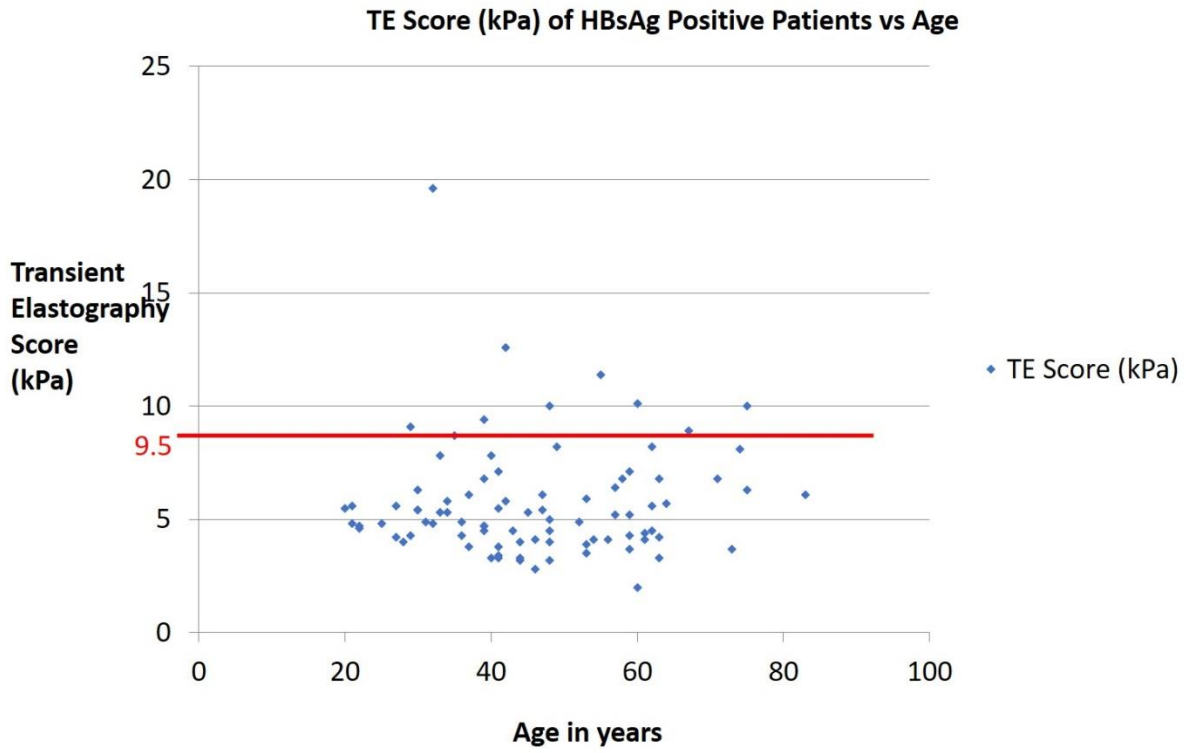


Figure 15: Scatter graph of Transient Elastography (Fibroscan®) scores versus age in HBsAg positive patients. A score ≥ 9.5kPa (red line) is considered severe fibrosis and carries an increased risk of progression to cirrhosis (TE score ≥ 12.5kPa).

The Pearson correlation coefficient is 0.0407 – this shows no association between age and fibrosis score in this population which is not significant (p-value 0.71).

Six patients were measured as having a TE score of ≥9.5 kPa (range 10-19.6 kPa). 5 patients were from Bradford and 1 from East London. 3 were born in Pakistan, 1 born in Nigeria, 1 born in Poland and 1 born in Latvia. Age range was 32-75 years.

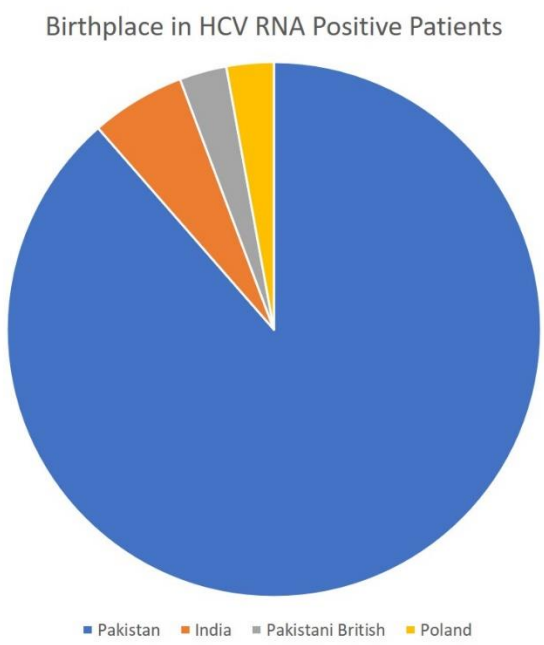
4.6 Demographics of Patients Testing HCV Ab Positive

94 (94·6%) of 94 patients with an HCV Ab positive result completed a diagnostic assessment: 59 were HCV RNA undetectable (one of whom was also HBsAg positive) and, of the 35 patients with viraemic HCV 35 attended imaging appointments. Of these, 20 (57.1%) were female, and 15 (42.8% male. 30 (85.7%) patients had HCV genotype 3 and five (14·3%) patients had liver cirrhosis.

Table 20: Demographic, Diagnostic and Imaging outcomes of HCV RNA positive Patients

Page 1	Gender	Age	Location	Country of Birth	Genotype	US Findings	Fibroscan® Score (kPa)	Treatment	Outcome
1	Female	32	Bradford	Pakistan	3A	No Cirrhosis	5.1	IFN/Ribavirin	Awaited
2	Male	35	Bradford	Pakistan	3A	No Cirrhosis	N/A	IFN/ Ribavirin	SV24 achieved
3	Male	39	Bradford	Pakistan	3A	No cirrhosis	10.8	IFN/Ribavirin	SV24 achieved
4	Female	29	Bradford	Pakistan	3A	No cirrhosis	4.2	IFN/Ribavirin	SVR12 achieved
5	Male	36	Bradford	Pakistan	1	N/A	1.5	DAAs	SVR12 achieved
6	Male	40	Bradford	Pakistan	3A	N/A	9.9	Await DAAs	
7	Male	27	Bradford	Pakistan	3A	No Cirrhosis	6.2	IFN/Ribavirin	SVR24 achieved
8	Female	28	Bradford	Pakistan	3A	No Cirrhosis	5.9	Await DAAs	
9	Male	46	Bradford	Pakistan	3K	No cirrhosis	4.8	IFN/Ribavirin	Responder-Relapser
10	Male	37	Bradford	Pakistan	3A	No cirrhosis	7.4	IFN / Ribavirin	Awaited
11	Male	43	Bradford	Pakistan	3A	No Cirrhosis	6.0	IFN/Ribavirin	SVR24 achieved
12	Female	82	Bradford	Pakistan	3A	No Cirrhosis	13.1	Await DAAs	
13	Female	38	Bradford	Pakistan	3A	No cirrhosis	6.1	IFN/Ribavirin	SVR24 achieved
14	Female	22	Bradford	Pakistan	3A	No cirrhosis	5.6	Await DAAs	
15	Female	49	Bradford	Pakistan	3A	No Cirrhosis	7.7	IFN/Ribavirin	Awaited
16	Female	37	Bradford	Pakistan	3A	No Cirrhosis	6.5	IFN/Ribavirin	Awaited

Page 2	Gender	Age	Location	Country of Birth	Genotype	US Findings	Fibroscan® Score (kPa)	Treatment	Outcome
17	Female	68	Bradford	Pakistan	3A	No cirrhosis	7.1	IFN/Ribavirin	SVR24 achieved
18	Female	47	Bradford	Pakistan	3A	No cirrhosis	N/A	IFN/Ribavirin	Awaited
19	Male	47	Bradford	Pakistan	3A	No Cirrhosis	4.6	IFN/Ribavirin	Awaited
20	Female	51	Bradford	Pakistan	1B	No Cirrhosis	3.6	IFN/Ribavirin	SVR24 achieved
21	Female	27	Bradford	Pakistan	3A	No cirrhosis	5	Await DAAs	
22	Male	27	Bradford	Pakistan	3A	No cirrhosis	N/A	IFN/Ribavirin	SVR24 achieved
23	Female	41	Bradford	Pakistan	3A	No Cirrhosis	N/A	Await DAAs	
24	Female	70	Bradford	Pakistan	3A	No Cirrhosis	6.2	Await DAAs	
25	Female	37	Bradford	Pakistan	3A	No cirrhosis	5.8	IFN/Ribavirin	SVR24 achieved
26	Male	31	Bradford	Pakistani British	1	No cirrhosis	N/A	DAAs SOF/LED	SVR12 achieved
27	Female	45	Bradford	Pakistan	3A	No Cirrhosis	16.5	IFN/Ribavirin	Responder-Relapser
28	Female	40	Bradford	Pakistan	3A	No Cirrhosis	7.4	IFN/Ribavirin	SVR24 achieved
29	Female	51	Bradford	Pakistan	3A	No cirrhosis	6.1	IFN/Ribavirin	Null responder
30	Male	38	Bradford	Pakistan	3A	No cirrhosis	7.3	IFN/Ribavirin	SVR24 achieved
31	Female	32	East London	India	3A	No Cirrhosis	N/A	IFN/Ribavirin	SVR24 achieved
32	Female	34	East London	India	1B	No Cirrhosis	4.9	DAA SOF/LED	SVR12 achieved
33	Male	35	East London	Pakistan	3A	No cirrhosis	20.6	IFN/Ribavirin	SVR24 achieved
34	Male	42	East London	Pakistan	3A	No cirrhosis	5.2	Await DAAs	
35	Male	34	East London	Poland	4	No cirrhosis	3.9	DAA Elb/Graz	Awaited



Birthplace by Country in HCV RNA Positive Patients

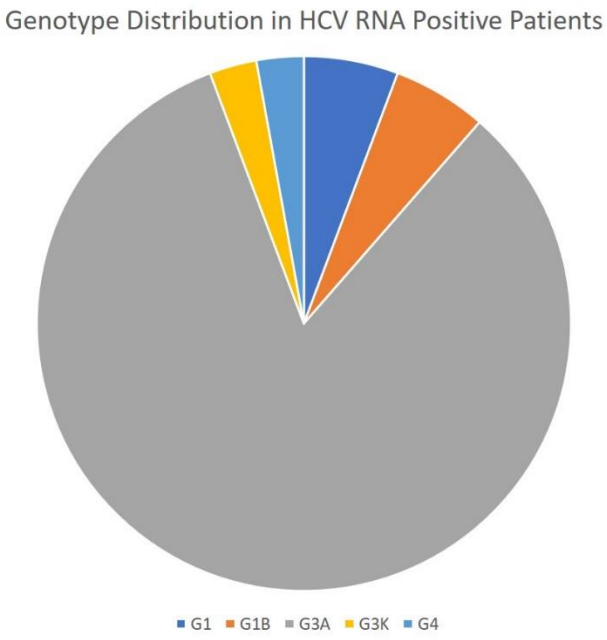
Pakistan = 31/35 (88.6%)

India = 2/35 (5.7%)

Pakistani British = 1/35 (2.8%)

Poland = 1/35 (2.8%)

Figure 16a: Birthplace of HCV RNA positive patients



Genotype 1 = 2 (5.7%)
Genotype 1B = 2 (5.7%)
Genotype 3A = 29 (82.8%)
Genotype 3K = 1 (2.9%)
Genotype 4 = 1 (2.9%)

Figure 16b: Genotype Distribution in HCV RNA Positive patients

Table 21: HCV Genotype Distribution by Birthplace

Hepatitis C Genotype	Country of Birth			TOTAL
	Pakistan	**India**	**Poland**	
G1	2	0	0	2
G1B	1	1	0	1
G3A	28	1	0	29
G3K	1	0	0	1
G4	0	0	1	1
TOTAL	32	2	1	35

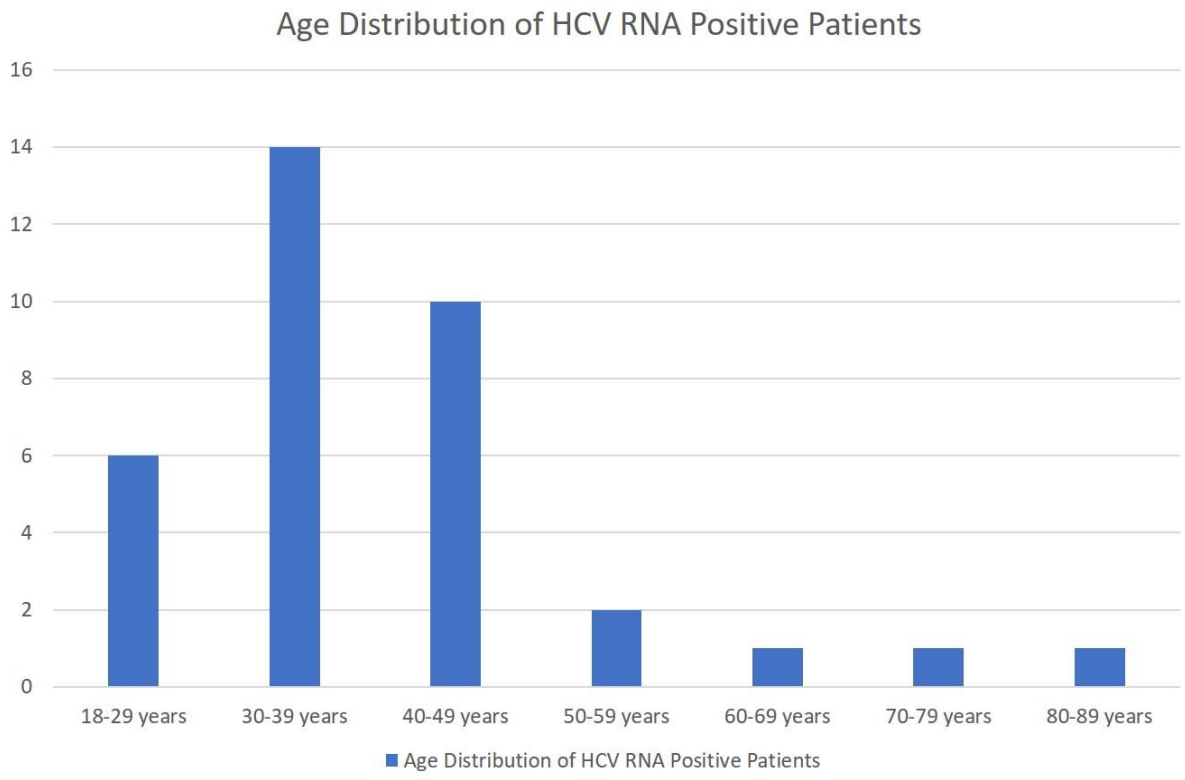


Figure 16c: Age Distribution of HCV RNA positive patients

35 patients tested HCV Ab and RNA positive. 20/35 (57.1%) were female, with the vast majority of patients (32/35, 91.4%) from Pakistan. Again, this is reflective of the local demographics of Bradford, where the majority of patients tested. The age distribution was skewed towards those aged <50 years (30/35), suggesting that testing in this age range in migrant populations will detect chronic viraemic HCV infection.

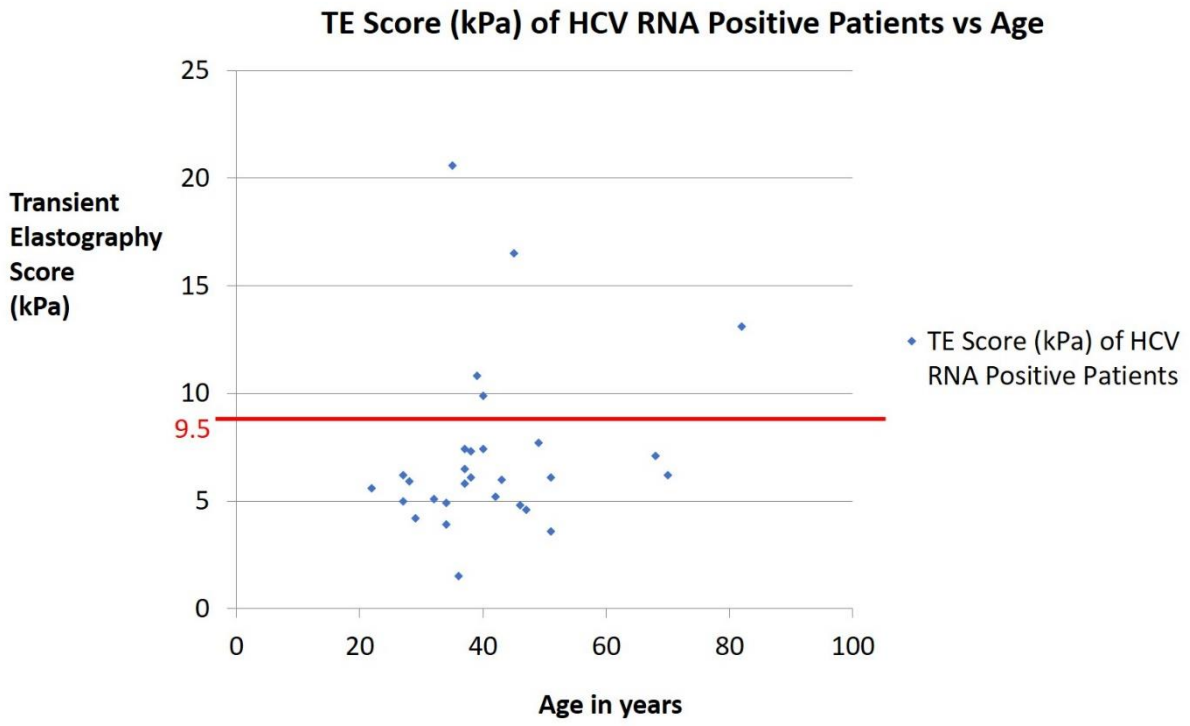


Figure 17: Scatter graph of Transient Elastography (Fibroscan®) scores versus age in HCV RNA positive patients. A score ≥ 9.5kPa (red line) is considered severe fibrosis and carries an increased risk of progression to cirrhosis (TE score ≥ 12.5kPa).

The Pearson correlation coefficient is 0.2116 – this shows weak association between age and fibrosis score in this population which is not significant (p-value 0.27).

Five patients were measured as having a TE score of ≥9.5 kPa (range 9.9-20.6 kPa). 4 patients were from Bradford and 1 from East London. All 4 patients were born in Pakistan. Age range was 35-82 years.

4.7 Patients found to have Severe Liver Fibrosis or Cirrhosis on Imaging

In total 13 /128 (10.1%) of patients were found to have liver cirrhosis on either liver ultrasound, Fibroscan® (value >9.5 kPa) or both.
Cirrhosis = on US or FS > 9.5 or both = 13 patients
US cirrhosis = 4 patients (two with FS > 9.5 kPa) – all HBsAg positive
Fibroscan® score >9.5 kPa (cirrhosis) = 11 (9 with no cirrhosis on US) – 5 HCV RNA positive, 6 HBsAg positive

Therefore total number = 2 with cirrhosis on FS and US, 2 with cirrhosis on US alone, 9 with cirrhosis on FS alone.

4.7.1 Liver Biopsy

22 patients (17 HCV positive, 5 HBsAg positive) underwent liver biopsy in Bradford, as per local protocols. This was part of standard investigation in the early part of the trial, but no patients in London were offered biopsy, as non-invasive studies (i.e. ultrasound and transient elastography) had taken precedence for investigation of viral hepatitis. As the intervention was not offered uniformly to all patients, the outcomes were not analysed for this dataset.

4.7.2 Management Plans for Patients with Severe Liver Fibrosis or Cirrhosis and HBV infection

The management plans for the 8 patients with HBV Infection and liver cirrhosis were:
1 patient was offered treatment with NRTIs (Entecavir). This patient continued to engage in therapy and achieved a viral load reduction by >80% within 3 months of starting treatment.
2 patients had cirrhosis on US but a low Fibroscan® score (4.5 kPa) with normal LFTs and VL<2000 copies/mL. Therefore the local MDT decision was for observation and repeat Ultrasound scan within 3 months.
5 patients with Fibroscan® score > 9.5 kPa but no cirrhosis on US, and normal LFTs and VL <2000 copies/mL had a plan to observe only.

4.7.3 Management Plans for Patients with Severe Liver Fibrosis or Cirrhosis and HCV Infection

All 35 patients with viraemic HCV were offered treatment either with currently available therapies or to await DAA treatment when available on the NHS.

The management plans for the 5 patients with HCV Infection and severe liver fibrosis or cirrhosis were:

3 patients were treated with Interferon-based therapies. 2 patients achieved SVR24 and cure, one patient had a responder-relapse outcome.
The other 2 patients opted to wait for the availability of new DAA drugs and were observed.

4.8 Discussion

Screening for chronic disease is a valuable measure of disease prevalence but is not in itself a means to an end. Screening should be offered in populations who are at risk of significant health problems from the condition. For viral hepatitis, the health problems include development of liver fibrosis, cirrhosis and hepatocellular carcinoma.

The HepFREE trial found a positivity rate of 1.98% (237 patients) for viral hepatitis in a population of 11,929 tested patients from 58,512 eligible migrants (20.3% tested) living in Bradford and London.

Of 220 positive patients from intervention practices, 84.5% (186/220) attended diagnostic assessments, of which 132 were invited to imaging assessments. Of the 128 patients who engaged in diagnostic and imaging assessments, 13 (10.1%) were found to have severe fibrosis or cirrhosis on ultrasound or transient elastography. An additional 2 patients (1.56%) were HDV co-infected, and 5 patients (3.9%) tested positive for HBeAg (a marker of increased HBV replication).

A majority of patients testing HCV Ab positive had cleared virus (58/93, 62.3%). Of note, the viraemic patients (0.3% of all tested) skewed towards younger age groups with the majority aged <50 years (30/35, 85.7%). It is not clear whether this is due to higher rates of viral clearance in elderly and otherwise healthy migrants or related to our eligible population being less likely to be tested for viral hepatitis in primary care as they have normal liver function tests. However, treating and curing a younger population will have impactful quality of life years (QALYs) for cost-effectiveness calculations.

All of the patients who tested positive had not previously been tested for viral hepatitis and did not have clinical markers indicative of liver disease (e.g. abnormal liver function tests) which may have led their GP to consider viral hepatitis screening. In 10% of these patients their severe liver fibrosis or cirrhosis would have been missed without the testing offered in the HepFREE trial, putting them at risk of developing undetected hepatocellular carcinoma. Testing asymptomatic migrant patients for viral hepatitis in primary care allows early detection of cirrhosis in this at-risk group.

These results show that the vast majority of patients will attend diagnostic and prognostic assessment after testing positive in primary care screening. This may be because they are self-selecting population and are already engaged with health promotion. Patients in this population

also attended for non-invasive staging by Fibroscan® which was an offered as an alternative to the more invasive liver biopsy procedure. In East London, Fibroscan® and ultrasound appointments were on two additional days following the diagnostic appointment visit, whereas in South London all these visits could be arranged for the same date – however this did not affect the uptake of the imaging assessment at both sites.

Engagement with diagnostic and prognostic appointments was 100% in patients with viraemic HCV patients. The reasons for this may be that patients were encouraged to attend for the opportunity be offered a curative therapy, or that at this point in HCV treatment in the UK (2015-2017) there was a strong push for case-finding from healthcare professionals with increasing access to the new DAA drugs.

During this timepoint, DAAs for the treatment of non-cirrhotic Genotype 3 HCV infection were not widely available in NHS services. This led to a delay in therapy for 8 patients with G3A infection. 17 patients with G3A infection opted to be treated with interferon-based therapy.

This underlines that any screening programme should have safe and effective treatment available for the underlying condition should it be detected. In the case of viraemic Hepatitis C, the treatment landscape has changed considerably in the UK in the last 5 years, with the NHS now entering an interferon-free treatment era, with DAAs now widely available and accessible for all genotypes. Better access to DAA therapy has been a strong promoter for increased case finding for hepatitis C in at-risk populations.

Several patients who were eligible for HBV treatment according to EASL guidelines on their baseline serology were not offered treatment (or treatment was deferred). This was due to local multi-disciplinary team decisions following two sets of serological results 3 months apart and in one case a patient was lost to follow-up after the decision to offer treatment.

Ongoing engagement in care in either secondary care or community care will be explored in the next chapter. Facilitators and barrier to offering viral hepatitis serology testing in primary care will be explored in the qualitative research presented in Chapter 6. The factors leading to patients attending for screening will be explored in the pre-screen survey outcomes presented in Chapter 7.

5. Results: London Community Clinic vs Standard Follow-up Clinic Trial

5.1 Introduction

In this chapter I present the results for the HepFREE Follow-Up Trial which randomised patients to follow-up in community based viral hepatitis clinics or standard of care (hospital-based clinics).

I will present a more detailed breakdown of outcomes at the London Community Clinics which was the aspect of HepFREE trial set-up and led by myself.

5.2 HepFREE Follow-Up Trial Results

A total of 128 pts tested positive for HBsAg (93) or HCV RNA (35), attended diagnostic and imaging appointments and progressed to ongoing follow-up in the HepFREE trial.

Of these 128, 90 patients were in Bradford, 19 in East London and 19 in South London. Initially it was planned that consent for the randomisation of each patient to their cluster allocation would be sought verbally. However, the ethics committee recommended that patients should provide written consent for randomisation. This required blinding of the clinical staff members in Bradford and London to the cluster allocations, so that they could consent patients. The protocol amendment for the addition of consent prior to follow-up in HepFREE community trials was in version 7 (dated Sept 2015), however some patients in Bradford and London had already tested positive and were not prepared to wait for cluster allocation prior to starting treatment or management. Therefore no community clinics were set up prior to protocol amendment version 7 in September 2015. Those patients had been randomised by cluster to community but declined to wait for the consent process were allocated to standard care. This group of patients are considered “Pre-Consent”

Therefore, by cluster randomisation:

Bradford – 41 standard, 49 community

East London – 8 standard (1 declined consent), 11 community (5 pre-consent and therefore standard by default, 1 declined and therefore standard by default, 5 community)

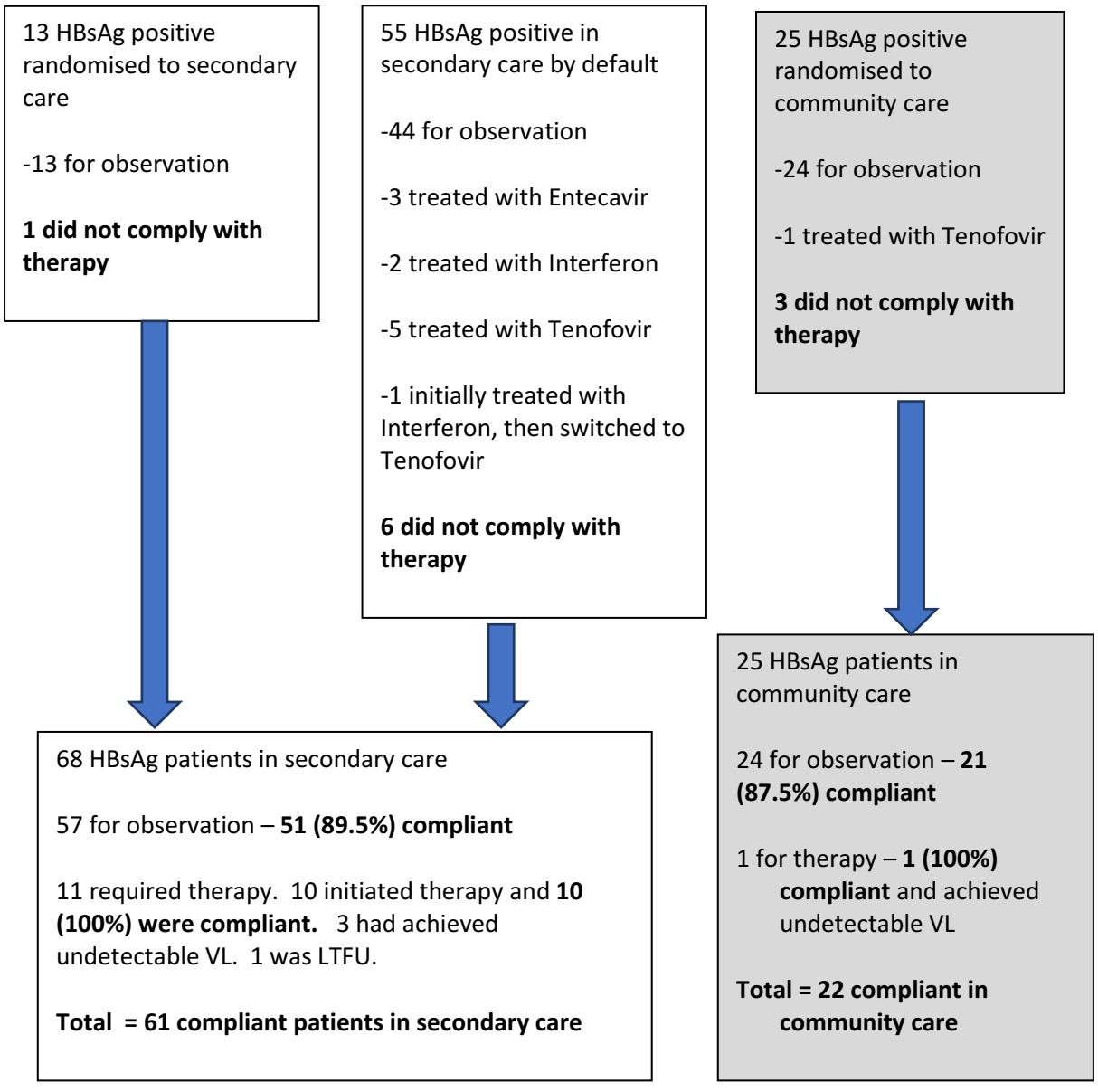
South London – 5 standard (two declined consent), 14 community (2 declined consent, 1 pre-consent).

The breakdown of all the patients in the HepFREE trial who attended community care was analysed by myself for engagement and treatment outcomes and are presented in Flow Charts 01 and 02, which also incorporates data presented in Table 4.1 in the previous chapter.

Table 22 Breakdown of Randomisation / Declined Consent / Pre-Consent Patients

	Bradford	**East London**	**South London**	**TOTALS**
Consented to Randomisation	22	12	16	**50**
Declined Consent	0	2	3	**5**
Pre-Consent	68	5	0	**73**
TOTALS	**90**	**19**	**19**	

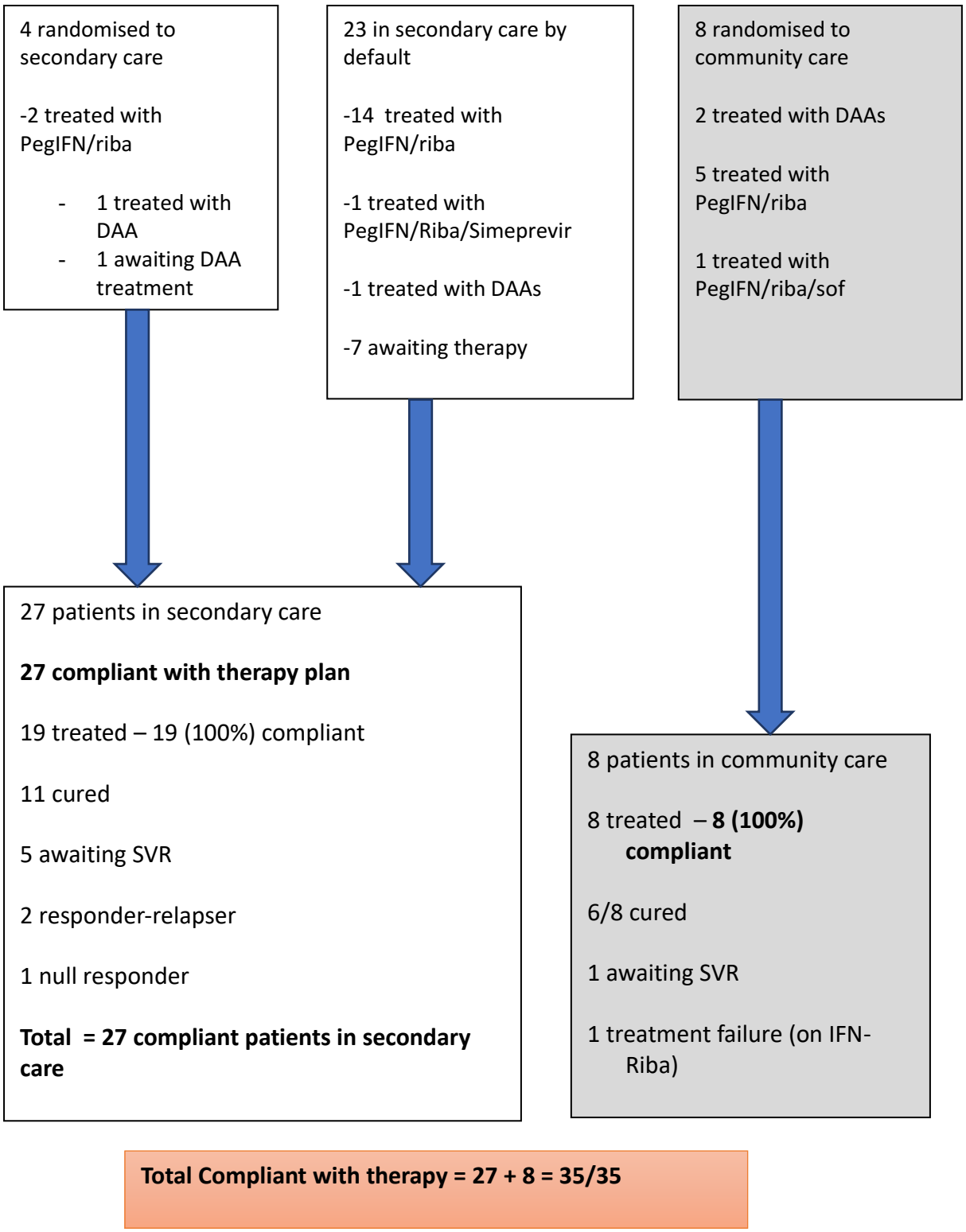
Figure 18 Management Plans and Outcomes for HBsAg positive patients



Total HBsAg positive patients compliant with therapy =

61 + 22 = 83/93

Figure 19 Management Plans and Outcomes for HCV Ab and RNA positive patients



5.3 Analysis of the HepFREE Follow-Up Trial

128 (58·1%) of 220 patients testing positive for viral hepatitis engaged in diagnostic and prognostic assessment (93 patients with HBV and 35 patients with HCV). Engagement with the diagnostic and prognostic assessment did not differ significantly between the groups; in an intention-to treat analysis, 80 (87·9%) of 91 patients receiving standard care engaged with diagnostic and prognostic assessment compared with 105 (81·4%) of 129 patients receiving community care (94 patients with HCV and 89 patients with HBV; IRR 0·76, 95% CI 0·2–2·5; p=0·65).

I then performed further exploratory analysis of the London based patients in the follow-up trial to look in more detail at the attendance and engagement of patients in this sub-cohort.

5.4 London Cohort Results

5.4.1 Randomisation per protocol vs Allocation in actuality

Of 38 patients in London, 13 were cluster randomised as per protocol to Standard follow-up and 25 to community follow-up.

However, the allocation in actuality was

(i) of 13 randomised to Standard follow-up – 3 declined to consent (but remained in Standard arm).

(ii) of 25 in Community care – 6 were randomised to community follow-up pre-consent and therefore defaulted to standard care, 3 declined to consent and defaulted to standard care, and 16 remained in community care.

Therefore the post consent final allocation in actuality was 22 to standard follow-up and 16 to community follow-up.

5.4.2 Demographics of Patients testing HBsAg and HCV AB positive in London

I analysed the 38 London patients by virus, gender, age and country of birth.

Of 38 London patients, 33 were HBsAg positive, and 5 HCV RNA positive. Prior to the introduction of consent for randomisation 25 (65.8%) of these patients would have been randomised to community-based care. The final allocation of patients saw 16 (42.1%) in the community-based care arm.

Table 23 Demographics of Patients testing positive for viral hepatitis in London

	Gender	Age	HBV or HCV	Country of Birth	Cluster Randomisation	Final Allocation
1	Female	27	HBV	Romania	Standard	Standard
2	Male	20	HBV	Romania	Community	Pre-Consent
3	Male	75	HBV	Nigeria	Community	Pre-Consent
4	Male	29	HBV	India	Community	Pre-Consent
5	Male	39	HBV	Bangladesh	Community	Community
6	Male	39	HBV	India	Community	Declined
7	Male	29	HBV	Moldova	Community	Community
8	Male	73	HBV	Pakistan	Standard	Standard
9	Male	44	HBV	Somalia	Standard	Declined
10	Male	74	HBV	Pakistan	Community	Community
11	Male	62	HBV	Pakistan	Community	Community
12	Male	34	HBV	Bangladesh	Standard	Standard
13	Female	37	HBV	Bangladesh	Standard	Standard
14	Male	57	HBV	Pakistan	Standard	Standard
15	Male	41	HBV	Ivory Coast	Standard	Standard
16	Male	37	HBV	Poland	Community	Standard
17	Male	71	HBV	Vietnam	Community	Standard
18	Male	39	HBV	Sierra Leone	Community	Community
19	Female	41	HBV	Bulgaria	Community	Community
20	Male	43	HBV	Sierra Leone	Community	Community
21	Female	40	HBV	Sierra Leone	Community	Community
22	Male	48	HBV	Ghana	Standard	Standard
23	Female	63	HBV	Sierra Leone	Community	Community

24	Male	53	HBV	Nigeria	Community	Community
25	Male	59	HBV	Vietnam	Community	Community
26	Male	49	HBV	Ghana	Community	Declined
27	Male	59	HBV	Ghana	Community	Community
28	Male	30	HBV	Albania	Community	Community
29	Female	46	HBV	China	Community	Community
30	Female	33	HBV	Ghana	Community	Community
31	Male	59	HBV	Nigeria	Standard	Declined
32	Male	41	HBV	Ghana	Standard	Declined
33	Male	47	HBV	Nigeria	Standard	Standard
34	Female	32	HCV	India	Community	Pre-Consent
35	Female	34	HCV	India	Community	Pre-Consent
36	Male	35	HCV	Pakistan	Community	Community
37	Male	42	HCV	Pakistan	Standard	Standard
38	Male	34	HCV	Poland	Standard	Standard

5.4.3 HBsAg Positive Patients

The 33 HBsAg positive patients in London were born in a total of 15 different countries – this is in contrast to the 10 countries of birth for the 60 HBsAg positive tested in Bradford. 26 were male and 7 female. The age range was 20-75 years with a median of 43 years.

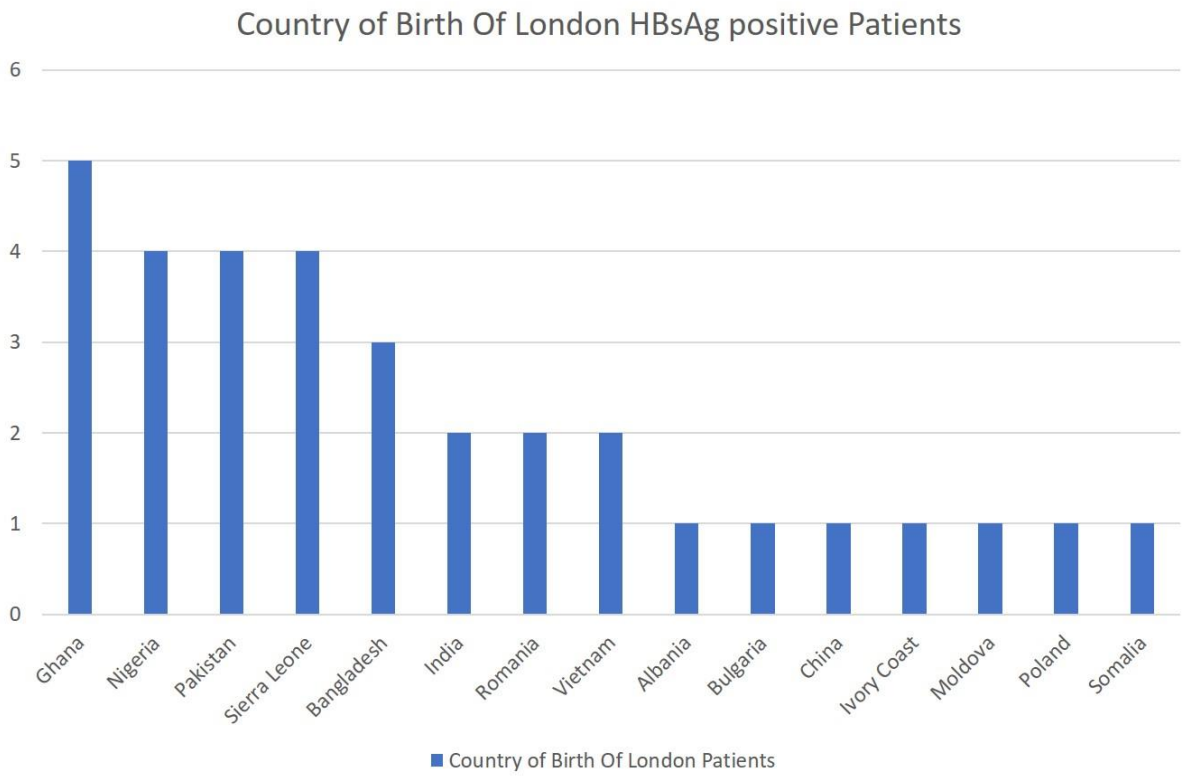


Figure 20: Country of Birth of HBsAg Positive Patients in the London Follow-Up Trial

5.4.4 HCV RNA Positive Patients

Of the 5 HCV RNA positive patients, 3 were male and 2 female. The age range was 32-45 years, with a median of 34 years. 2 patients were born in India, 2 born in Pakistan and 1 born in Poland.

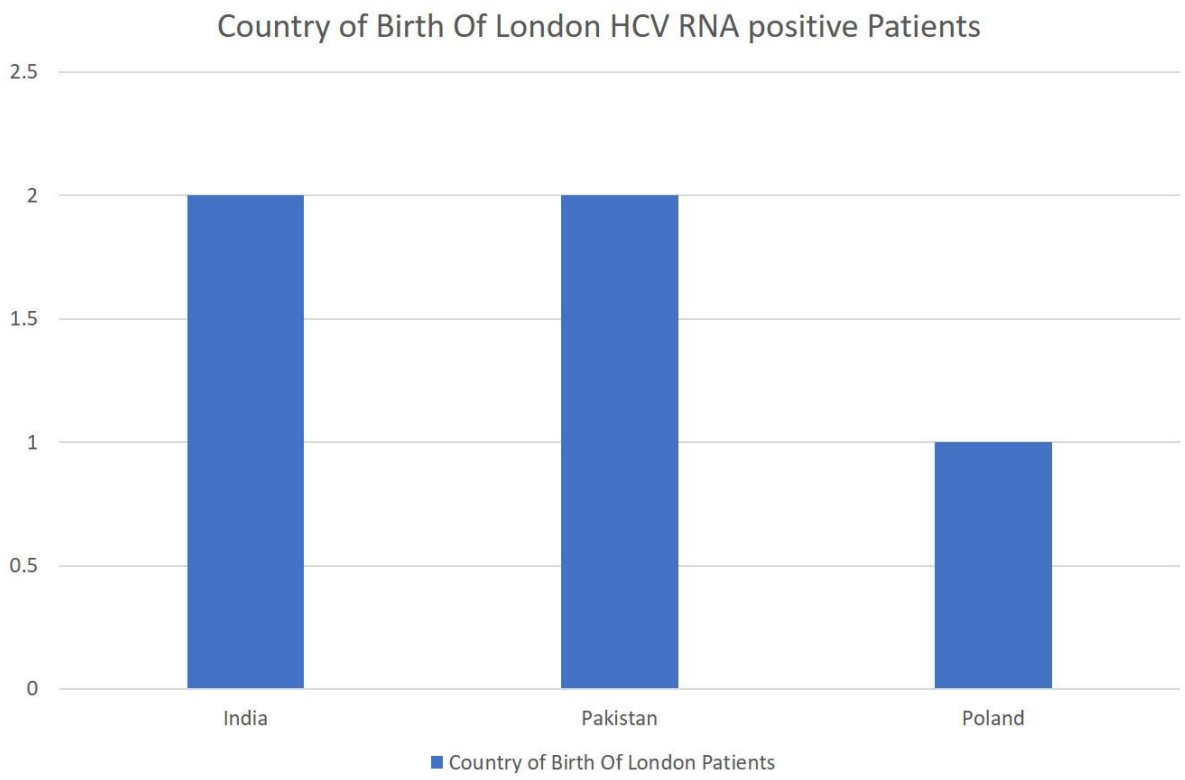


Figure 21: Country of Birth of HCV RNA Positive Patients in the London Follow-Up Trial

5.4.5 Total Patients Randomised to Community Care Post-Consent

Following the Follow-Up Trial Consent Amendment, 16 patients who consented to randomisation were randomised to the community arm of the follow-up trial. 5 patients were in East London and 11 in South London, 11 were male and 5 female and 15 of the patients were HBV positive, and 1 was HCV RNA positive.

5.4.6 Community Clinic Attendances

The community clinics in East and South London were based at 6 GP Practices from November 2015 until February 2017. Engagement in Community Care was deemed to be attendance at one appointment after randomisation. Further appointments for individual patients were scheduled for their ongoing viral hepatitis care during the duration of the trial, ending in February 2017. This was in order to develop the scope of the trial to assess if patients would attend community appointments to for ongoing care.

A total of 37 appointment slots were offered to the 16 patients across 28 clinical sessions on 27 calendar days. There were 30 attendance from the 37 appointment slots (81%).

One patient who did not attend 2 appts in a row was deemed to be lost to follow-up to community care and subsequently defaulted to secondary care. This patient also did not attend further secondary care appointments. Therefore 15/16 (93.8%) patients engaged in community care as per the trial protocol.

5.4.7 Treatment Outcomes in the Community Clinics

Of the 16 patients randomised to community clinic care, the management plans were:

14 patients for observation (all HBsAg positive patients with no cirrhosis, normal LFTs and VL <2000).

1 patient for treatment with NRTIs (HBsAg positive, no cirrhosis with age > 40, ALT>30 and VL>20,0000). This patient was treated with Tenofovir and achieved a > 80 reduction in VL within 3 months.

1 patient for treatment with Interferon (HCV RNA positive, and cirrhosis on US and Fibroscan®). This patient was seen at two community-based appointments whilst on Interferon treatment – however as this patient developed biochemical hyperthyroidism, as per protocol his follow-up care defaulted to secondary care.

1 patient for observation who did not attend appointments.

Table 24: Community-Based Viral Hepatitis Clinics in London

Date of Clinic			Venue of Clinics and number of patients (attended / appointments)					
Year	**Month**	**Date**	**East London**			**South London**		
			Jubilee Street	**Dr Abiola**	**St Andrews**	**Sir John Kirk**	**Albion Street**	**Manor Place**
2015	**Nov**	**25th**		1/1				
2016	**Jan**	**19th**		1/1				
	Feb	**25th**	1/1					
	March	**4th**				0/1		
	April	**8th**				1/1		
	May	**6th**					1/1	
		19th	1/1					
	June	**17th**				0/2		
		28th				0/1	1/1	
	July	**29th**					1/1	
	Aug	**11th**				1/1		
	Sept	**9th**				2/2		
		15th	1/1					
		29th			1/1			
	Oct	**4th**		1/2				
		7th					1/1	
		11th					3/3	
		18th		0/1				
		20th						2/3
	Nov	**11th**					1/1	
2017	**Jan**	**12th**				1/1		
		17th		1/1				
		19th						1/1
	Feb	**3rd**				2/2		
		4th					1/1	
		10th				1/1		
		17th					1/1	
		22nd			1/1			
TOTALS			3/3	4/6	2/2	8/12	10/10	3/4
				30 attendances to 37 appointment slots				

5.4.8 Standard Care Attendances

The standard care clinics in East and South London were based at Barts Health in East London (Royal London Hospital, Whitechapel and Whipps Cross Hospital, Leytonstone) and King's College Hospital from September 2015 until February 2017. Engagement in Standard Care was deemed to be attendance at one appointment after randomisation. Further appointments for individual patients were scheduled for their ongoing viral hepatitis care during the duration of the trial, ending in February 2017. This was in order to develop the scope of the trial to assess if patients would attend standard care appointments to for ongoing care.

A total of 41 appointment slots (see table) were offered across two sites in East London and one in South London.

A total of 41 appointment slots were offered across 30 clinical sessions on 30 calendar days to the 22 patients. There were 35 attendance from the 41 appointment slots (85%).

One patient who did not attend 2 appts in a row was deemed to be lost to follow-up to secondary care. Therefore 21/22 (95.5%) patients engaged in standard care as per the trial protocol.

5.4.9 Treatment Outcomes in the Standard Clinics

Of the 22 patients randomised or defaulted to standard clinic care, the management plans were:

15 patients for observation (all HBsAg positive patients with no cirrhosis, normal LFTs and VL <2000).

2 patients for observation who did not attend appointments.

2 patients for treatment with Interferon (both HCV RNA positive), one of whom achieved SVR24 and the other achieved SVR12 by study end date.

1 patient for treatment with NRTIs (HBsAg positive, HBeAg positive, no cirrhosis with age > 40, ALT 28 and VL>20,0000). This patient was treated with Tenofovir and achieved a > 80 reduction in VL within 3 months.

1 patient (HCV RNA positive) opted to await treatment with DAAs dependent on NHS availability.

1 patient (HCV RNA positive) was eligible for a Drug research trial with access to DAAs and opted to pursue this as a treatment course after attending the engagement appointment in HepFREE follow-up.

Table 25: Standard Care Viral Hepatitis Clinics in London

Date of Clinic			Venue of Clinics and number of patients (attended / appointments)		
Year	**Month**	**Date**	**East London**		**South London**
			Royal London Hospital	**Whipps Cross Hospital**	**King's College Hospital**
2015	**Sept**	**28th**			1/1
	Oct	**7th**	1/1		
2016	**Jan**	**20th**	3/3		
	Feb	**10th**	1/1		
	April	**20th**	3/4		
	May	**4th**	1/1		
	May	**13th**			1/1
		1st	1/1		
	June	**22nd**	2/2		
		6th	1/1		
	July	**8th**			1/2
		13th	1/1		
		27th	1/1		
	Aug	**5th**			0/1
		10th	1/1		
		24th	1/1		
		28th			1/1
	Sept	**2nd**			1/1
		16th			0/1
		30th			2/2
	Oct	**5th**	2/2		
	Nov	**1st**		1/1	
		4th			1/1
		9th			1/1
		11th	1/1		
		17th			1/1
	Dec	**7th**	0/1		
2017	**Jan**	**6th**			1/1
		20th			2/2
	Feb	**8th**	1/2		
	TOTALS		**21/24**	**1/1**	**13/16**
			35 attendances to 41 appointments		

Table 26: Comparison of Patient engagement in Standard and Community Care

	Engaged Patients / Total Patients		**Totals**
	East London	**South London**	
Standard Care	14/14	7/8	21/22
Community Care	4/5	11/11	15/16

Table 27: Comparisons of attendances in Standard and Community Care

	Attendance / Appointments		
	East London	**South London**	**TOTALS**
Standard Care	22/25	13/16	**35/41 (85.4%)**
Community Care	9/11	21/26	**30/37 (81.1%)**

5.5 DISCUSSION

Patient engagement after diagnosis is an important consideration when developing a new case-finding intervention. Keeping patients engaged with ongoing care is particularly important for a chronic healthcare problem such as chronic Hepatitis B infection which involves six-monthly check-ups for serology and/or ultrasound imaging. Both Hepatitis B and C infection also represent a public health concern, and improving patient engagement in care reduces the wider public health exposure. Patients living with viral hepatitis have traditionally represented a "hard-to-reach" group, often because they do not engage on an ongoing basis with healthcare services. It is not clear if migrant populations also fall into a poorly engaging group, and so the HepFREE follow-up trial was devised to test the hypothesis that patients are more likely to attend locally provided viral hepatitis at a nearby primary care centre rather than standard care based in the local hospital.

A total of 128 patients who attended their diagnostic and imaging appointments were eligible for randomisation for follow-up in the HepFREE follow-up trial.

73/128 of the patients were not randomised for the follow-up trial as their engagement and management occurred before the protocol v7 amendment which required written consent for randomisation as part of the ethical approval for this part of the trial. All of these patients defaulted to standard care and were followed-up and recorded as standard care patients. 5 patients expressed a strong preference for hospital care and declined to consent for randomisation. In each case this was noted to be because they perceived that hospital-based care would be more specialist and suited to their needs, despite being advised that the same clinicians would be seeing them if they were randomised to community care within this trial.

The remaining 50 patients were randomised after consent, and as a result 33 patients were randomised to the community arm of the trial. As this was statistically underpowered, the data was analysed on an intention to treat basis. Engagement in both arms was excellent at >80%, and there was no statistical difference in engagement between the two groups.

It should also be noted that two patients who consented to randomisation and whose care was arranged for follow-up on the community were found in post-hoc analysis of the screening to have been not eligible for the trial. This was because their country of birth was incorrect on GP records (stating UK instead of true country of origin) and they happened to have been tested opportunistically by their GP in uncapped intervention practices. One of these patients was HCV RNA positive and eligible for DAA therapy, and achieved SVR12 in the community viral hepatitis clinic. The other patient was HBsAg positive and treated with tenofovir in a community hepatitis

clinic, successfully achieving a viral load decay of >80% within 3 months. Although their data has not been presented here, the process of arranging their care informed my experience in setting up novel community based viral hepatitis services.

Setting up community care viral hepatology clinics allowed me to reflect upon the challenges and benefits posed by this novel way of delivering care.

Benefits for the healthcare professionals included the involvement of the multi-disciplinary team and engagement with primary cares services. In order to set up the 6 community clinics in London, I worked with specialist nurses, specialist pharmacists, local research teams and the Operational Delivery Network at Barts Health (Royal London and Whipps Cross) and King's College London. This included discussions about the patients' management, arranging transfer of medication from hospital pharmacy to local GP practices, and ensuring the correct serology bottles were used for blood tests. Medical management was a particular issue – at first it was thought that DAA drugs may be able to be stored on site at the GP practice, but when the numbers of patient appointments were 1-2 per sessions, it was felt to be too risky to leave expensive drugs in the community should the patients not attend for their appointments. To avoid losing drugs, any transport of DAAs was done door-to door from hospital pharmacy to GP practice by myself by private taxi service. Where transport of DAAs was not involved, public transport was used. Although NRTI drugs are much cheaper than DAAs, their transport was handled in a similar way.

The main difference between the set-up of community clinics and standard care clinics was that standard care hospital clinics were set in one site on one day of the week, and HepFREE patients were seen in one appointment of sixteen in a session (4 appointments in 4 hours).

Community clinics, on the other hand, occurred on variable days of the week for a much smaller number of appointments (1-3). These days and times were arranged for the patients' convenience, but also involved liaising with the GP practice to ensure a room was available for the clinic. On one occasion I arrived with a patient to a GP practice which was closed for the afternoon – the administrative staff who had confirmed the HepFREE session had forgotten that a clinic training session was arranged for the same time. (Fortunately, on that occasion I was allowed to use a room for the purpose of the HepFREE appointment).

Venepuncture was performed by myself in community clinics and involved transport of samples back to the hospital lab – for standard care patients their serological testing was performed by healthcare assistant on site.

Patients attending standard care were routinely sent a text reminder 48 hours prior to the appointment. In the community care arm, patients may have been seen at a GP practice other than the one they were registered at – therefore they were reminded of the appointment and location by phone call by me 48 hours prior to the appointment. This was an additional task to ensure community-based patients had a similar reminder to patients in standard care. As patient numbers were low and the appointment times and dates not necessarily predictable, it was difficult to delegate this task to an administrative member of staff or another research team member. Managing the community cohort across 6 sites in London required organisation, planning and flexibility in re-arranging missed appointments.

The data shows that there is no significant difference in engagement between the standard care and community care arms of the follow-up trial. The main limitation of this analysis is the small numbers of patients who consented to randomisation and were seen in the community care arm. However, the logistics, management and organisation required for arranging community care for small numbers of patients was much more involving for myself as their clinician than for patients seen in standard care. The HepFREE Follow-Up trial suggests that community-based care is not required for this population who are health-engaged after being diagnosed with viral hepatitis, and its benefits are hard to ascertain when engagement with standard care follow-up was so good. At this time-point in HCV treatment there was also a perception from some patients that being seen in the community may lead them to "miss out" on treatment with the new DAA drugs, and there may be an ongoing perception in this population that community based care is somehow substandard to hospital care. Patient perception would be an area worthy of qualitative research should the idea of primary care-based hepatitis clinics be explored in the future. At present, our data suggests that clinical resources would be better used in standard based care for patients identified in general practice screening sessions.

6. Results: Patient Pre-Screening Survey

6.1 Introduction

In this chapter I present my analysis of the pre-screening survey of patients eligible for viral hepatitis from four interventional screening practices in North East London, South East London and Bradford.

Prior to HepFREE screening beginning in 2014, a survey of patients eligible for viral hepatitis testing was performed by the qualitative researcher John Owiti to investigate patients' illness perceptions regarding viral hepatitis. I collated and cleaned the data and linked the survey data to the HepFREE outcomes I collected during the screening trial. I then performed descriptive analysis and logistic regression of the survey data with the assistance of a statistician from QMUL. The aim was to test the hypothesis that patients' understanding of viral hepatitis and its impact on health indicates whether or not they will attend for screening when invited.

For full methods please see section 2.5 of Chapter 2.

6.2 Participation Outcomes

1935 eligible patients were identified from the GP record from 4 practices and contacted by the research team to enquire about their interest in participating in a survey about knowledge and attitude to viral hepatitis infection. Patients were contacted by an invitation letter and follow-up phone-call. Patients were unable to participate in the study for various reasons including declining participation and not being contactable for an invitation by letter or phone. The full list of reasons for eligible patient drop-out and the numbers this included are outlined in the Flow Chart 1.

At the end of the recruitment process, a total of 377 of 1935 eligible patients (19.1%) agreed to complete a pre-screening survey. Of those who did not participate, 208 declined participation, and a further n=1350 did not respond to attempted contacts from the study team (see flowchart 1).

The survey was conducted by postal survey (self-completed by the patient) or by telephone interview (with the researcher collecting the responses).

Of the 377 patients who agreed, 7 patients returned postal surveys which did not have any responses to the demographics or knowledge base questions. These 7 were not included in the analysis.

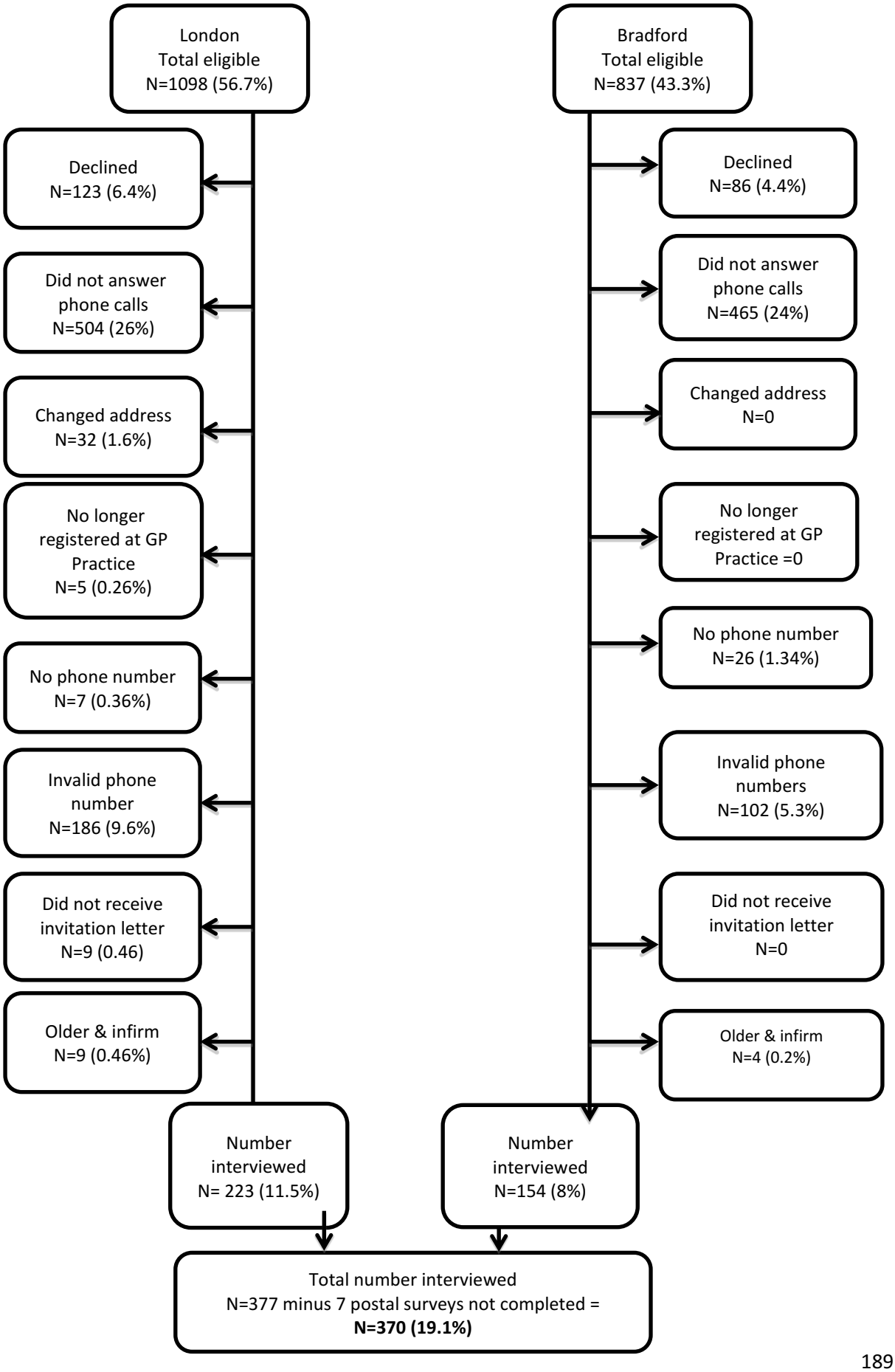
A sample of the survey questions is included in Appendix 11.

Interviewees were asked about their demographics (age, gender, ethnicity, birthplace) and understanding and knowledge of viral hepatitis (including symptoms, transmission, knowledge of treatments and vaccinations). The respondents were also asked questions regarding mood and

anxiety in order to assess PHQ and GAD scores. Finally, participants were asked about their willingness to test for viral hepatitis having been informed of their eligibility for testing.

Outcomes of the data were assessed with the primary outcome being the number of patients who took-up the screening invitation by close of recruitment at their practice. Testing outcomes for the screened patients were cross-checked with the screened population data.

Figure 22: Flow chart of the patients eligible for the pre-screen survey



6.3 Survey Results

Of 377 patients who consented to be interviewed, 370 completed the survey in full.

377 patient identifiers were collated on the OpenClinica database, of which 370 had survey data collected. 7 patients returned postal surveys which did not have any responses to the demographics or knowledge base questions.

The 370 patient identifiers were cross-checked with the HepFREE screening data. 147 participants were from Bradford, 192 were from South London and 31 were from East London.

92/370 participants attended for HepFREE screening for viral hepatitis. In Bradford 73/147 (49.6%) participants attended, in South London 13/192 (7.3%) attended, and 6/31 (19.4%) of East London participants attend.

None of the 92 screened participants tested positive for HBsAg or HCV AB.

Table 28: Survey Respondents and Attendance for HepFREE Screening

Location	Survey Respondents	Attended for HepFREE Screening (%)	Tested positive at screening
Bradford Practice 1	77	25 (32.5%)	0
Bradford Practice 2	70	48 (68.5%)	
Bradford TOTAL	147	73(49.6%)	0
East London	31	6 (19.4%)	0
South London	192	13 (7.3%)	0
BRADFORD + LONDON TOTALS	370	92 (24.9%)	0

Table 29: Comparison of Pre-Screening Testing Uptake with total HepFREE Screening Trial Outcomes

Group Tested in HepFREE	Pre-Screen Interviewees At Intervention Practices (2014)		HepFREE Outcomes at Intervention Practices (2014-2017)
Total Tested	92/370 = 24.9%		11,929/58,512 = 19.5%
<40 years tested	35/194 = 18%		5151 / 36,115 = 14.3 %
≥40 years tested	57/176 = 32.4%		6,235/22,397 = 27.8%
African tested	16/177 = 9%		545/6866 = 11.7%
Pakistani tested	38/120 = 31.7%		6,841 / 19,001 = 32.5%

It is notable how similar the outcomes of screening uptake were in the pre-screening survey population compared with the main HepFREE outcomes in all the parameters above.

6.3.1 Demographics

The records of the 370 participants were analysed by the following parameters:

Demographics:

- Gender
- Ethnicity
- Age
- Place of birth
- Average PHQ-7 score
- Average GAD score

Responses to personal history and knowledge of viral hepatitis screening and treatment were also analysed. Parameters in these fields were

- A personal history of testing for viral hepatitis
- A personal history of being vaccinated against hepatitis B infection
- A family history of viral hepatitis infection
- Knowledge of treatments for viral hepatitis.

Table 30: Demographics of Respondents

Demographics		TESTED (n=92)	DID NOT TEST (n=278)
Gender	Male	40 (43%)	120 (43%)
	Female	52 (57%)	158 (57%)
Ethnicity	African	18 (19.6%)	161 (57.9%)
	Pakistani	73 (79.3%)	82 (29.5%)
	Chinese	----	26 (9.4%)
	White	----	7 (2.5%)
	Indian	1 (1.1%)	2 (0.7%)
Place of Birth	South Asia	50 (54.3%)	53 (19.1%)
	UK & Ireland	22 (23.9%)	-----
	Africa	18 (19.6%)	166 (59.7%)
	Middle East	2 (2.2%)	1 (0.36%)
	China	----	26 (9.4%)
	Europe	----	32 (11.5%)
Age	18-39 years	35 (38%)	158 (57%)
	40+ years	57 (62%)	110 (39.7%)
	Not recorded	----	10 (3.6%)
	----------	----------	----------
	Mean Age	45.4 years	38.8 years
	Mode by decade	50-59 years	30-39 years

Place of birth:

For the purposes of descriptive analysis, country of birth was collapsed to continents as below:

- South Asia (Pakistan, India)
- Africa (Ghana, Somalia, Eritrea, DRC, Ivory Coast, Nigeria, Sierra Leone, South Africa, Guinea, Algeria, Zimbabwe, Uganda, Senegal, Kenya, Gambia, Ethiopia, Cameroon, Angola)
- Middle East (Saudi Arabia, Afghanistan)
- UK & Ireland
- China
- Europe (UK, Germany) – NB this combination was for the Did Not test group only

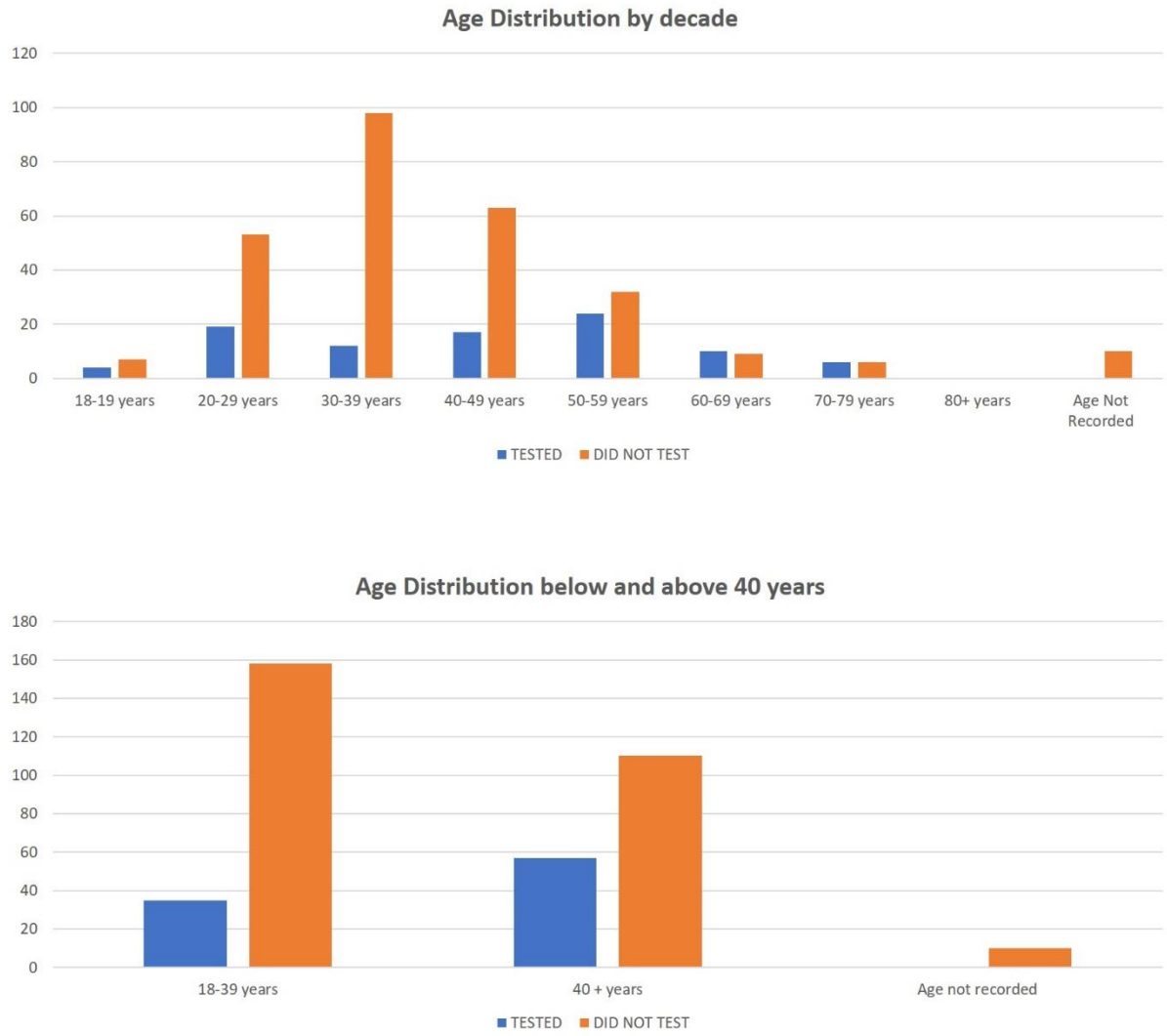


Figure 23: Age distribution of respondents

6.3.2 Depression and Anxiety Scores of Respondents

Table 31: PHQ-9 and GAD-7 Scores of respondents

Depression & Anxiety Score		TESTED (n=92)	DID NOT TEST (n=277)
PHQ-9 Score	0-4 – No depression	57 (58.7%)	194 (69.8%)
	5-9 – Mild depression	19 (20.7%)	45 (16.2%)
	10-14 – Moderate depression	9 (9.8%)	19 (6.8%)
	15-20 – Moderate to severe depression	6 (6.5%)	15 (5.4%)
	20+ Severe depression	1 (1.1%)	5 (1.8%)
GAD-7 Score	0-4 – No anxiety	64 (69.5%)	210 (75.5%)
	5-9 – Mild anxiety	11 (12%)	34 (12.2%)
	10-14 – Moderate anxiety	9 (9.8%)	18 (6.5%)
	15+ - Severe Anxiety	8 (8.7%)	16 (5.8%)

6.4 Regressive Analysis

I was interested in whether the likelihood in attendance for testing could be predicted according to demographics such as ethnicity or place of birth, and if there was a relation to other factors such as mental health status, or knowledge related to viral hepatitis.

A cross-tabulation of the data allowed a binary logistic regression to be performed against the outcome of uptake vs non-uptake.

Data was prepared as follows:

Binary Data (0/1 according to no/yes response) was prepared for the following variables to be analysed using the Stata program:

21 x symptoms variable

25 x consequences

19 x perceived treatments

34 x perceived causes

5 x historical items (including previous screening, familial risk, HCP recommendation)

1 x screened/not screened

PHQ and GAD scores were categorised for sensitivity analyses and descriptive tests.

Ethnicity was categorised dependent on the most common values.
Frequencies for each variable were run for screening uptake and screening drop-out.

An assumption of logistic regression analyses is a minimum expected cell count of 5. After an initial descriptive analysis for these variables, it was found that some categories needed collapsing down before the counts could be run as logistic regressions.
As a result of this the consequences variables were converted to binaries instead (i.e. a score of 1 to 8 will collapse to 1).
- Perceived biological consequences (0-8; sum of liver cancer, liver cirrhosis, death, lifelong infection, exhaustion, high blood pressure, stomach ulcer, depletion of energy)
- Perceived social consequences (0-8; loss of employment, loss of future income, stigma, shame, not being able to marry, killed by family, discrimination, isolation)
- Perceived psychological consequences (0-7; worry, stress, fear, anxiety, sadness, depression, fear of getting liver cancer)
Other variables were also collapsed as outlined in Table 32.

Variable	Full List of responses		Collapsed Version	Final Collapsed Version
Ethnicity	African Algerian Angolian Cameroonian Chinese Congolese Eritrean Ethiopian Gambian Ghanaian Guinean Indian Ivorian Kenyan Malawian	Nigerian Other African Pakistani Senegalese Sierra Leonian Somalian South African Sudanese Ugandan White White European White South African White/Black South African Zimbabwean	African Pakistani Chinese Other	African Pakistani Other
Country of Birth	Algeria Angola Cameroon China DR Congo Eritrea Ethiopia Gambia Germany Ghana Guinea India Ivory Coast	Kenya Malawi Nigeria Pakistan Saudi Arabia Senegal Sierra Leone Somalia South Africa Sudan Uganda UK Zimbabwe	Africa Pakistan Chine UK/Ireland Middle East India Germany	African Pakistan/India UK/Ireland Other
Age	Range 18-79		18-39 / 40-79	
PHQ	Range 0-27		None Mild Moderate Moderate/Severe Severe	None Mild Moderate-Severe
GAD-7	Range 0-21		None Mild Moderate Moderate/Severe Severe	None Mild Moderate-Severe
Marital Status	Single Engaged Married Living as Married Separated Divorced Widowed		Single Married / Living as Married / Engaged Separated / Divorced Widowed	
Aware of Treatments	Yes / Unsure / No		Yes / No	

Table 32 Collapsed Demographic and PHQ/GAD variables for logistic regression analysis

6.4.1 Binary Logistic Regression Analysis

Regression analysis was run on the variables in the following groupings:

(i) Demographics

(ii) PHQ9 and GAD-7 Scores

(iii) History of personal viral hepatitis testing or family member with infection or tested

(iv) Willingness to test or be vaccinated (vs HBV)

(v) Understanding of viral transmission, symptoms and treatments

(vi) Perception of consequences of viral infection.

These analyses were run for the interview participants who subsequently tested in the HepFREE trial (n = 92), and for those who stated they were willing to test but subsequently did not test (n=226). Results are presented in Tables 33-38.

Table 33 Logistic Regression Analysis of Demographics of Participants

Variable			Tested (n=92)					Willing to Test but Did Not Test (n=226)				
		n	OR	p	95% CI			n	OR	p	95% CI	
Age (at 2014)	**18-39 (REF)**	35	------	------	-----	-----		111	------	------	-----	-----
	40-79	57	2.21	0.00	1.36	3.59		115	0.63	0.11	0.35	1.12
Gender	**Male**	40	1.01	0.96	0.63	1.63		100	1.21	0.52	0.68	2.17
	Female (REF)	52	------	------	-----	------		126	------	------	-----	-----
Ethnic Group	**African (REF)**	16	------	------	-----	-----		97	------	------	-----	-----
	Pakistani	73	8.51	0.00	4.67	15.50		111	0.13	0.00	0.06	0.27
	Other	3	0.61	0.52	0.13	2.76		18	0.80	0.79	0.16	4.06
Birthplace	**Africa**	16	0.14	0.00	0.07	0.30		99	6.86	0.00	2.82	16.67
	Pakistan/India	50	1.33	0.40	0.68	2.60		75	0.93	0.85	0.43	2.02
	Other	4	0.10	0.00	0.02	0.47		13	------	------	-----	-----
	UK / Ireland (REF)	22	------	------	-----	-----		39	------	------	-----	-----
Marital Status	**Single**	11	------	------	-----	-----		48	------	------	-----	-----
	Married/Living as married/Engaged	73	3.35	0.00	1.69	6.66		157	0.33	0.01	0.14	0.77
	Separated / Divorced / Widowed	8	2.45	0.07	0.92	6.54		21	0.55	0.15	1.97	
Location	**Bradford (REF)**	72	------	------	-----	-----		103	------	------	-----	-----
	East London	6	0.27	0.01	0.10	0.69		19	2.85	0.06	0.96	8.51
	South London	14	0.08	0.00	0.04	0.15		104	10.76	4.91	23.60	

Where Odds Ratio >1.00 and p<0.05:

- Over 40s are more likely to screen

- Pakistani pts are more likely to screen than African respondents; those born in Pakistan are less likely to drop out of screening after invitation than those born in the UK.

- Conversely, African pts are less likely to screen and more likely to drop out after invitation than the Pakistani group.

Table 34 Logistic Regression Analysis of PHQ9 & GAD7 Scores of Participants

Variable		Tested (n=92)						Willing to Test but Did Not Test (n=226)				
		N	OR	p	95% CI			n	OR	p	95% CI	
PHQ9	None (REF)	58	-------	------	-----	-----		139	-------	------	-----	-----
	Mild	18	1.44	0.25	0.78	2.65		46	0.71	0.34	0.35	1.44
	Moderate	9	1.61	0.27	0.69	3.76		21	0.75	0.57	0.28	2.01
	Moderate/Severe	7	1.19	0.71	0.48	2.96		20	1.13	0.83	0.38	3.32
GAD7	None (REF)	63	-------	------	-----	-----		159	-------	------	-----	-----
	Mild	12	1.06	0.87	0.51	2.21		30	1.30	0.58	0.52	3.23
	Moderate	9	1.64	0.25	0.70	3.83		19	0.54	0.20	1.44	
	Severe	8	1.14	0.76	0.49	2.67		18	0.79	0.66	0.28	2.23

There was no statistically significant correlation between presence (or absence) of symptoms of low mood or anxiety and subsequent attendance for screening.

Table 35 Logistic Regression Analysis of History of Testing Scores of Participants

Variable		Tested (n=92)						Willing to Test but Did Not Test (n=226)				
		n	OR	P	95% CI			n	OR	p	95% CI	
Previously Tested	No (REF)	60	-----	-----	-----	-----		133	-----	-----	-----	-----
	Yes	13	0.42	0.01	0.22	0.82		29	1.66	0.28	0.66	4.18
	Don't Know*	15	0.47	0.02	0.25	0.89		60	2.31	0.03	1.09	4.87
Family has tested	No (REF)	58	-----	-----	-----	-----		131	-----	-----	-----	-----
	Yes	13	0.69	0.28	0.35	1.37		22	1.22	0.70	0.44	3.37
	Don't Know	21	0.58	0.06	0.33	1.02		73	1.61	0.15	0.84	3.10
Family with HBV/HCV	No (REF)	59	-----	-----	-----	-----		160	-----	-----	-----	-----
	Yes	17	3.58	0.00	1.72	7.43		25	0.37	0.03	0.16	0.88
	Don't Know	16	1.14	0.68	0.61	2.15		41	0.74	0.43	0.35	1.57

*Four respondents (screened) and four respondents (did not screen) did not complete this question.

Participants with a family member living with viral hepatitis were more likely to attend for screening after invitation than those without.

Table 36 Logistic regression of Willingness to test/vaccinate/follow recommendation

Variable		Tested					Did Not Screen				
		n	OR	p	95% CI		n	OR	p	95% CI	
Willing to Test	No (REF)	32	------	-------	-----	-----	------	------	-----	-----	----
	Yes	226	1.24	0.62	0.53	2.90					
	Undecided	5	------	-------	-----	-----	-----	-----	-----	----	----
Willing to vaccinate	No (REF)	29	------	-------	-----	-----	6	-----	-----	----	----
	Yes	235	1.64	0.33	0.60	4.47	179	0.90	0.75	0.45	1.78
	Undecided	20	------	-------	-----	-----	12	-----	-----	----	----
Recommended by HCP	No (REF)	318	------	-------	-----	-----	213	-----	-----	----	----
	Yes	45	0.64	0.28	0.29	1.44	8	1.20	0.82	0.24	6.13
	Unsure	5	------	-------	-----	-----	0	-----	-----	----	----

Table 37 Logistic Regression of Knowledge

Variable		Tested (n=92)					Willing to Test but Did Not Test (n=226)				
		n	OR	p	95% CI		n	OR	p	95% CI	
HBV/HCV Caused by Virus	No (REF)	66	--------	-------	-----	-----	49				
	Yes	26	1.18	0.84	0.22	6.24	23	1.07	0.94	0.18	6.32
HBV / HCV causes liver cancer / diseases	No (REF)	57	--------	-------	-----	-----	146				
	Yes	35	1.12	0.66	0.69	1.82	80	0.72	0.27	0.40	1.29
Knowledge of relevant symptoms	No (REF)	40	--------	-------	-----	-----	104				
	Yes	52	1.14	0.58	0.71	1.84	122	0.75	0.32	0.42	1.33
Aware of Treatments	No (REF)	36	--------	-------	-----	-----	122				
	Yes	51	1.87	0.01	1.16	3.02	96	0.55	0.04	0.31	0.97
	Unsure	5	--------	-------	-----	-----	8				
Treated at Hospital	No (REF)	52	--------	-------	-----	-----	127				
	Yes	40	0.93	0.76	0.58	1.49	99	1.18	0.57	0.66	2.11
Treated spiritually	No (REF)	82	--------	-------	-----	-----	193				
	Yes	10	0.73	0.39	0.35	1.52	33	1.34	0.50	0.57	3.15
Treated with traditional medicine	No (REF)	74	--------	-------	-----	-----	186				
	Yes	18	1.17	0.61	0.63	2.17	40	0.83	0.61	0.40	1.72

Table 38 Perception of Consequences of Viral Hepatitis Infection

Variable		Tested (n=92)					Willing to Test but Did Not Test (n=226)				
		n	OR	P	95% CI		n	OR	p	95% CI	
Perceived biological consequences	No (REF)	39	-------	-------	-----	----	87	-------	-------	-----	----
	Yes	53	0.72	0.19	0.45	1.17	139	1.38	0.28	0.77	2.47
Perceived psychological consequences	No (REF)	53	-------	-------	-----	-----	127	-------	-------	-----	----
	Yes	39	0.98	0.92	0.61	1.57	99	0.91	0.75	0.51	1.62
Perceived social consequences	No (REF)	57	-------	-------	-----	-----	141	-------	-------	-----	----
	Yes	35	1.08	0.75	0.67	1.76	85	0.98	0.96	0.54	1.78

Looking at the variables associated with knowledge of viral hepatitis and perceptions of the consequences of infection, only one variable was associated with screening uptake which was knowledge of treatments. This indicates that improving patient knowledge of new therapies should improve screening uptake and should be prioritised over other knowledge areas.

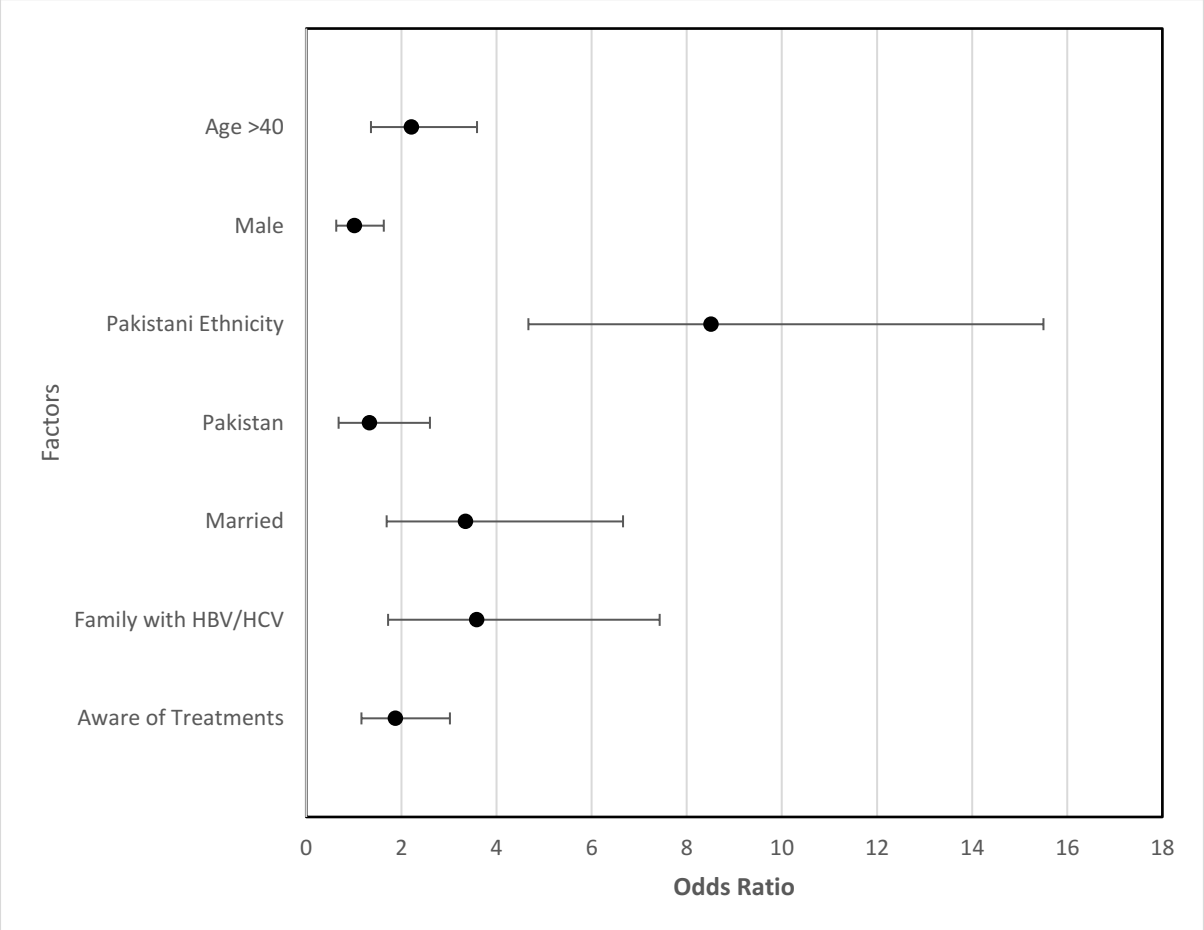


Figure 24 Forest Plot of Odds Ratio with Confidence Intervals against statistically significant variables

6.4.2 Stratified Regressive Analysis

Finally, the significant bivariate regressions were analysed by location and ethnicity strata groups. These stratified regressions showed that significant effects when accounting for location strata are mostly explained by ethnicity.

Table 39 Descriptives for Ethnicity groups by intervention location

	Location	**African**	**Pakistani**	**Chinese/Other**	**Total**
n	Bradford	2	146	6	154
%		1.30	94.81	3.90	100.00
n	East London	16	13	2	31
%		51.61	41.94	6.45	100.00
n	South London	158	0	33	191
%		82.72	0.00	17.28	100.00
n	Total	176	159	41	376
%		46.81	42.29	10.90	100.00

The majority of Bradford participants identified as Pakistani.

East London participants mostly identified as African or Pakistani.

The majority of South London participants identified as African.

Table 40 Awareness of treatments and likelihood of screening

Screened	OR	Std Err	Z	P>z	95% CI	
Aware of treatments						
Yes	1.87	0.45	2.59	0.01	1.16	3.02
No	0.25	0.04	-8.11	0.00	0.18	0.35

Table 41 Awareness of Treatments, Ethnicity and Location on likelihood of Screening

Screened	OR	Std Err	Z	P>z	95% CI	
Aware of Treatments						
Yes	1.06	0.29	0.19	0.85	0.61	1.82
Ethnicity						
Pakistani	8.68	2.73	6.87	0.00	4.69	16.08
Chinese/other	0.90	0.59	-0.17	0.87	0.24	3.27
African (REF)						
Location						
Bradford	1.06	0.30	0.22	0.83	0.61	1.84
East London	0.25	0.12	-2.89	0.00	0.09	0.64
South London	0.07	0.03	-7.63	0.00	0.04	0.15

The association of awareness of treatments was significantly explained by those who identified as Pakistani (where z-score is < -1.96 or > 1.96 and p-value <0.05), and also significantly explained by those in Bradford (majority Pakistani participants).

Table 42 Awareness of treatments on Dropout rates

Not Screened	OR	Std Err	Z	P.z	95% CI	
Aware of Treatments						
Yes	0.55	0.16	-2.05	0.04	0.31	0.97
No	3.19	0.66	5.64	0.00	2.13	4.78

Table 43 Awareness of treatment and ethnicity on dropout rates

No screened	OR	Std Err	Z	P.z	95% CI	
Aware of treatments						
Yes	0.92	0.31	-0.26	0.79	0.47	1.78
- **Ethnicity**						
Pakistani	0.13	0.05	-5.21	0.00	0.06	0.28
African	0.56	0.40	-0.80	0.42	0.14	2.31

Those aware of treatments were less likely to drop out.

The association of awareness of treatments on drop out was significantly explained by those who identified as Pakistani.

6.5 Discussion

This analysis of 370 participants eligible for the HepFREE Screening trial prior to the initiation of testing gives us an insight into the potential facilitators and barriers to patients agreeing to testing. The population is representative of the final screened population, with male/female, <40 years and >40 years and Pakistani and African patients well matched. Predictors for attending for testing were being Pakistani, over 40 years of age, knowing a family member with viral hepatitis and awareness of treatments.

24.9% of the interviewees attended for screening, compared to a 19.5% uptake in intervention practices in the main HepFREE screening trial. It is striking how similar the uptakes rates were in the pre-screening population with the general eligible population in the HepFREE trial, not only overall but also amongst <40 years and ≥40 years age groups and the African and Pakistani populations.

Pakistani patients attended for screening in 3:1 ratio compared to African (or Black) patients. The ratio was similar in the pre-screen population and suggests that patients from Pakistani backgrounds are more likely to be motivated to attend for viral hepatitis testing. Several reasons could explain this: (i) living in Bradford, Pakistani patients were more likely to be invited at uncapped intervention practices by their GP (ii) Pakistani patients may be more likely to know a familiar member with HBV or HCV. However, on the latter point, viral hepatitis positivity rates were similar in both ethnicities in the HepFREE trial (2.0% in Pakistani population, 1.7% in Black/African populations), so it may be that fewer Black African patients have an awareness of an affected family member.

Knowledge of treatments was another strong predictor of attendance for screening, and this may be more commonly found in patients who have already been aware of a family member or friend treated for viral hepatitis. Again, this was associated with Pakistani populations. Mood and perception of illness did not show any significant correlation with screening uptake.

How these findings are utilised in future viral hepatitis case-finding strategies will be explored in my discussion chapter.

7. Results: The HepFREE Provider Experience

7.1 Overview

As the main HepFREE screening trial recruitment came to a close, it became apparent that there was a wide variability in recruitment figures between practices (ranging from 3-30% of eligible patients). In order to understand this, the HepFREE Provider Substudy identified 12 intervention practices who would be invited to participate in qualitative research interviews. These practices were selected on the basis of their recruitment outcomes, as I wanted to interview participants from practices that had recruited >20% of eligible patients (high recruiters), <10% of eligible patients (low recruiters) and between 10-20% (intermediate recruiters).

These practices were identified as in Table 44.

HepFREE Screening Trial Recruitment Determinants

High: >/ = 20% of eligible patients

Intermediate: between 10.1-19.9% of eligible patients

Low: </= 10.0 % of eligible patients

7.2 Recruitment of HCPs for Qualitative Research

An initial email was sent to 14 HepFREE intervention practices for the recruitment of HCPs for interview. This email explained the role of qualitative research as part of the HepFREE trial and invited staff to participate in an anonymised 20-30min interview conducted either face to face or by phone for the purposes of understanding the facilitators and barriers to providing viral hepatitis screening in primary care.

Recruitment was extremely slow. After the initial email, and follow-up emails after two weeks and four weeks later, none of the practices responded with interest and on further questioning by telephone and in person while discussing other aspects of the trial, two respondents (practice managers) advised that many HCPs did not feel they had the time to provide further participation in the HepFREE Trial outside of the provision of screening intervention.

Therefore to encourage participation, ethical approval was sought for the provision of a £50 shopping voucher incentive to individual HCPs for their participation in the qualitative study.

From the initial contact of 12 practices, 9 practices responded to the call for interviewees. One practice HCP agreed to be interviewed but prior to signing the consent form was informed by their practice that the incentive should be a cash payment to the practice managers. As we did not have

ethical approval for this, the participant was asked if they would be happy to be interviewed in their own time at the HepFREE office. The participant initially agreed to this, but then withdrew before consenting to interview. Two other interested participants did not respond to further emails requesting a suitable interview time.

This left 8 interested respondents from 6 practices, and face to face and telephone interviews were arranged, according to individual preference.

Table 44 HepFREE Provider Experience Study Interviews

Location	Practice	Closure	Recruitment	Interviewer & Type	Interviewees	Interview Date
East London	Dr Patel	Aug 2015	High 789/1743 45.3%	Stuart Phone Interview	GP	May 2017
East London	Stratford Village	Oct 2015	Intermediate 74/650 11.4%	Stuart	Declined	
East London	Jubilee Street Practice	Oct 2015	Intermediate 94/500 18.8%	Stuart In person	GP + Practice Nurse & Receptionist	May 2017
East London	Royal Docks	July 2016	Low 50/500 10%	Dania	Declined	
East London	St Andrew's	April 2016	Low 88/500 17.6%	Stuart In person	Withdrew (HCA)	
South London	Sir John Kirk	June 2016	High 117/500 23.4%	Dania	Declined	
South London	Lambeth Walk	May 2016	Intermediate 64/475 13.5%	Dania Phone Interview	GP	May 2017
South London	Crown Dale	Feb 2016	Low 40/500 8%	Dania	Declined	
South London	Albion Street	Dec 2015	Low 178/2615 6.8%	Dania Phone Interview	Practice Nurse	May 2017
South London	Streatham Common	Jan 2016	Low 147/3954 3.71%	Dania	Practice Manager	May 2017
Bradford	Primrose	Dec 2015	High 1836/2984 61.5%	Stuart	Declined	
Bradford	Picton	Dec 2015	High 1696/1842 92.1%	Stuart	Declined	
Bradford	Valley View	Dec 2015	Intermediate 533/3189 16.7%	Stuart In Person	Healthcare Assistant	Feb 2017
Bradford	Moorside Surgery	Feb 2016	Intermediate 79/600 13.1%	Stuart	Declined	

INTERVIEW TOPICS

TOPICS 2014	TOPICS 2017
1. Practice Involvement in research	**Topic 1 Practice Background**
2. Technical Set-Up	1.1 Research Experience at the Practice
3. Training in Intervention Delivery	1.2 Awareness of Hepatitis at the Practice
4. Delivering the Intervention	
5. Recruiting and Consenting patients	**Theme 2 HepFREE Set-Up**
	2.1 Specific leads (designated)
	2.2 Technical set-up and prep
	2.3 Funding
	Theme 3 Delivering the Intervention
	3.1 Process
	Theme 4 Recruitment to the Study
	4.1 Staggered recruitment
	4.2 views on recruitment letter
	4.3 Opportunistic testing
	4.4 telephoning /texting patients
	4.5 language support provided
	4.6 communication with HepFREE team
	4.7 patient response
	4.8 consenting patients
	Theme 5 Perceptions of benefits and Outcomes
	5.1 Perception of Outcome
	5.2 Perceived benefits to patients & staff
	Theme 6 Perceptions of Challenges
	6.1 Demands on time/workload

7.3 2017 End of Trial Interviews

Seven interviews with eight healthcare practitioners were recorded over a four month period between February and May 2017 (see Table 44). One interview was a joint discussion with a practice nurse and receptionist; the others were one-to one interviews. Four interviews were via telephone and three were face to face.

Four interviews were performed by Interviewer 1 (myself) and three by Interviewer 2 (Dr Dania Shoeb, a GP trained in Qualitative Research). Both researchers had no previous direct contact with their allocated primary care practices.

The interview duration ranged from 6 min 46s to 24 min 28s. The interviews were subsequently transcribed and thematic analysis was used to identify important commonalities and differences within provider accounts.

7.4 2014 Pre-Trial Interviews

I wanted to use my 2017 end of trial interviews data to expand upon data from interviews conducted by the Qualitative Researcher Lorna Sweeney in July-October 2014 with 20 primary care staff from 14 practices (6 practices in Bradford, 8 practices in London). Nineteen were telephone interviews, with one participant interviewed face-to-face. Participants included:

- 5 General practitioners
- 4 Practice managers
- 4 Practice administrators
- 3 Healthcare assistants
- 2 Practice nurses
- 2 Practice IT leads

All study procedures were approved by the Research Ethics Committee at Queen Mary, University of London (No. QMREC2012/02). All participants provided verbal consent to the recording of their interview. Topic Guide for these interviews is in Box 2. Recordings were transcribed by Lorna Sweeney and identifying information removed for written transcripts. However, primary care practice identification was made available to me and one practice (Practice C) provided staff for interviews in both 2014 and 2017.

7.5 Thematic Analysis

I explored the key topics from the responses to my 2017 end of trial interviews, and then used these to expand on the similar topics covered in the 2014 responses to build a thematic analysis of interviews with interventional practice staff at two timepoints in the trial.

The topics that were explored in both sets of interviews are found in the Interview Topics Box-out.

7.6 Theme 1 Practice Background in Research

7.6.1 2014 Interviews

2014 participants were asked about the motivators for the practice to become involved in the HepFREE trial. For many interviewees, stated that the practices viewed the study as being very relevant to their patient population as they had a high volume of patients who met the eligibility criteria, and that this intervention had a role in reducing long-term health problems for their patients. There were anticipated benefits to patients which outweighed the burden of introducing a new screening programme. Some staff were surprised by the number of eligible patients identified at their practices:

"I think we were shocked really at how many people from such a wide range of countries it would affect. And we have quite a high Asian population, but we're also getting lots of new patients from Eastern Europe as well. So we thought it would be really useful for our patients and help them before things get too bad."

Practice administrator, Bradford primary care practice '2'

Another primary motivator was additional funding attained by being part of a research study and that this trial was suitable for their practice as it provided financial incentive for recruitment and acknowledged the extra strain on time and resources it would involve.

> *"And then the funding has to, it has to cover costs, plus a little bit to be honest. No GP at the moment is going to do something for goodwill, purely in research. Because we're so stretched, we just can't fit in anything else. And money is being eroded left, right and centre."*

GP, London primary care practice 7

At the time of the Early Interviews, practice staff voiced concerns that other regular duties of the clinic would take priority over a research project. Some interviewees noted that the study activation

had been delayed at their location until practice targets (such as annual flu vaccinations) had been completed.

> *"We had a lot of other things going on and a lot of changes going on for primary care…And so we had to keep switching between that and back onto the Hep and that sort of thing. But that was more to do with the timing of how it landed with other national requirements that were going on."*
>
> Practice manager, Bradford primary care practice A

> *"We've only sent a hundred [letters] out, because obviously with it being flu season, flu immunisations and stuff have to take priority."*
>
> Practice administrator, Bradford primary care practice N

7.6.2 2017 Interviews

Interview participants were asked about how much experience their practice and they themselves had in clinical research. Two interviewees described their practices as research practices, with one identifying their surgery as part of a primary care research network. Their previous experience in participating in clinical trials was a particular help in consenting patients for testing. For some of the healthcare providers the HepFREE trial was their first personal experience of providing care in the context of a clinical trial. This did not appear to impact recruitment outcomes – practices with no previous research experience were among the intermediate and high recruiters. One lead GP felt that as a research practice (who delivered a high recruitment outcome) they were especially interested as the topic was relevant to their patient population.

> *"I like breaking myths of "you can't do research with people who don't speak English as a second language, or who don't speak English, or that Bengali populations are not going to come forward". "Research is a challenge... What went well was it was a topic that is topical and relevant to this area"*
>
> Lead GP, London, Practice C

In the 2017 interviews, the benefit of the practices being part of a research network was highlighted, and although the extra work caused by the HepFREE trial was noted, most participants did not feel their regular practice duties were compromised by being part of this study.

7.7 Theme 2 HepFREE Trial Set-Up

7.7.1 2014 Interviews

Technical problems in developing the bespoke search terms the HepFREE team used to identify eligible patients on electronic patient records led to a delay in initiating the trial at some practices. There were further problems in and then monitoring screening uptake of recruited patients which meant search terms changed several times, causing confusion amongst primary care staff.

In 2014, several interviewees voiced frustration at some the early search design problems and felt this led to additional workload for practice staff. One IT lead created their own solution

> *"The searches that they built were totally incorrect; they haven't been able to identify the patients or taken into account anyone who declined to be tested for the study, or anyone who has already got hepatitis diagnosis. Now I've reported that to them and to our IT department multiple times, but they've not bothered to update the searches to take any consideration for...So we've had patients being rung three or four times to come for appointments and they've got a hepatitis diagnosis already, or they've already declined to be in the programme. It's quite a big problem really and I don't think we've got feedback or help regarding that at all…I ended up having to build my own searches to filter all this stuff out"*
>
> Practice IT lead, Bradford primary care practice C

Some participants voiced concern that the research team did not have a good understanding of the software already used in primary care practices and had not adequately tested the search terms in advance of implementing them at the practice.

> *"There seems to be some sort of issue with the software, but I think that really should have been sorted out initially. And one issue is they clearly don't have access to an EMIS computer so they can't really even test it on fake patients".*
>
> GP, London primary care practice M

7.7.2 2017 Interviews

In the end of trial interviews, participants reflected upon how the trial set-up had affected delivery of the study at the practice. Many interviewees felt having a specific lead GP was beneficial to provide direction. As the trial intervention was delivered over an 18 month period at each practice, the range of staff allocated to the study included Healthcare assistants, Data Quality mangers and

practice nurses as well as the Practice Manager. At one practice a medical student was recruited to assist with phlebotomy, and their duties included blood draws for the HepFREE trial. This had the effect of more staff groups feeling involved in trial delivery.

The HepFREE team provided a training session to each practice prior to activation in the trial. This included training on viral hepatitis, the consent process and explanation of the trial objectives. Lead GPs were tasked with cascading this information to new staff involved in the trial, and the HepFREE team were also available to repeat the training session if required.

Some variability was noted in the interviewees' experiences of the training process. Most of the participants reported a good training experience, highlighting that staff felt well informed about the trial and the consent process.

"We were well informed… training felt well done from start to finish."

Healthcare Assistant, Bradford, Practice A.

"Training experience was good… it was education, plus highlighting the importance of the research and how to do it"

Lead GP, London, Practice E

However HCP participants at one practice recognised that there were some gaps in their training – highlighting that this made it more difficult to explain the reasons for the trial to patients. At this particular practice the Lead GP recognised that cascading training model had not worked for them, and although the practice felt well supported by the HepFREE team, they struggled to ensure all staff were aware of the trial intervention and how to recruit patients.

"We had no training… (I'd have liked) a half day telling us the reason why we're doing it. Even though I've read it up, tell us why we're doing it - what we're capturing and how it will benefit the patients. So we can express it a bit more to them."

Practice Nurse, London, Practice C

"The only people that were trained were me, (plus) the deputy practice manager. So if (staff) say they didn't have any training, cos the training will have been a bit slapdash probably from me. Was I supported? Yes. Was the rest of the team supported? Probably no."

Lead GP, London, Practice C

At some practices, the HepFREE team were able to provide additional support from Clinical Research Nurses to consent and draw blood from recruited patients. This staff at Practice C felt that extra

support staff were helpful in providing the intervention, but this was not necessarily due to a lack of funding but staffing resources.

"(The HepFREE team) helped us by finding extra support. It wasn't usually a money thing, it was time thing, and a priority thing. Would we be happy to take part in a study like this again? Honest answer is no. The amount of work, time, extra effort that I did, I don't think I've got that time now."

Lead GP, London, Practice C

As well as a training session, practice leads for HepFREE were left a "site pack" with information on the study which included a manual for the practice and contact numbers of the HepFREE team. However, some interviewees felt that this was impractical, too long and not suitable for using to consult during the consent process. Some participants suggested as one-page summary poster to simplify the intervention would have been more practical for primary care.

Key messages from these responses were that all staff groups should be included in training sessions to minimise knowledge gaps for HCPs, and the provision of summery posters would be good reminders of the key aims of the intervention.

7.8 Theme 3 Delivering the Intervention

7.8.1 2014 Interviews

In the early stages of the trial, the process of delivering the intervention, after the initial eligibility searches had been completed, was described by the interviewees as "straightforward" and easy". Most practices used a healthcare assistant or nurse as the primary healthcare provider to consent and test patients. These duties were conducted as part of their regular clinic slots.

The extra workload was noted by some participants as a potential barrier to recruitment, but others felt it was less onerous than other previous studies they had been involved in. Some particularly liked that after training and electronic searches had been set-up, the practice was left alone to carry out the intervention and valued this autonomous direction.

"…it was well communicated. Even from the very start, of putting out the interest, to us accepting, to them coming and doing a talk, to then actually doing the clinics, getting trained up to do them, and ***then leaving us alone then, just to do it,*** *and then feedback and the results. It's all been pretty straightforward and smooth."*

Practice IT lead, Bradford primary care practice E

However, not all practices had the staff and resources to match the demand that HepFREE placed on their time. One participant voiced a concern that the HepFREE team should be providing external staff to carry out consent and testing at the practice, and if this was not available it may be difficult undertake for staff to manage the additional workload of recruiting patients.

7.8.2 2017 Interviews

Three years later at the end of trial recruitment, interviewees reflected on the resources needed by the practices and individual staff members to deliver the interventional screening. A wide range of expertise was mentioned, from administrative and IT skills to understanding date input and collection.

The role of an interpreter, or access to translating services at the practice, was one area several respondents viewed as being very important for screening migrant populations.

Languages offered by staff at practices included Bengali, Punjabi and Urdu, and other services included a local interpreters and patient advocates as well as the translation service Language Line. The absence of an interpreter was identified as reason that patients were not invited to test, as this would lead to a longer consultation and or another appointment.

> *"If it was a patient that didn't speak English, obviously we rely on language line, so it would mean having a consultation over the phone, which would we mean we would really need a longer appointment. Sometimes patients would come with a relative prepared to translate for them"*
>
> Specialist Nurse, London, Practice D

Collecting data from the trial involved coding patients as having consented to the trial and provided a blood sample with bespoke HepFREE Trial codes. The results from the blood screening would also be recorded in patient records and positive outcome were referred onto the HepFREE team for follow-up to be arranged. Data collection proved more burdensome for some practices than others, particularly those without a data manager. Collection of HepFREE recruitment and outcomes was described as "straightforward" by two of the interviewees, both of whom were from practices were administrative staff were used to inputting data, or had a data quality manager. Another practice respondent felt the process took longer to document than non-trial data, and another respondent found the bespoke codes difficult to remember.

7.9 Theme 4 Recruitment to the Study

7.9.1 2014 Interviews

Recruiting patients for screening

One of the biggest challenges faced by primary care practices was patient recruitment to the trial. At each practice, all identified eligible patients were invited by letter to screen for viral hepatitis. Practices were randomised to a standard invitation letter or an enhanced invitation letter which included a Patient information Leaflet (PIL) on viral hepatitis. Letters and PILs were written in the spoken language of the individual patients (according to their demographic data at the practice).

At the early stage interviews, the screening invitation letter was not perceived to be the most effective way to recruit patients. Participant felt that the patients are generally unlikely to read or act upon screening invitations, and also voiced a concern that this particular target population (at risk migrants) were likely to be mobile and may not receive the letter. Interviewees also thought knowledge of viral hepatitis to be poor amongst the target populations and therefore recipients may not identify themselves as being at risk of the infections, especially if they have UK residents for some time.

Interviewees felt that the HepFREE enhanced letter invitation was too lengthy and dense in its content.

Telephone invitations and opportunistic testing were highlighted as being more efficient and successful methods of recruitment to screening tests and health engagement generally.

> *"So what we did was we sent out letters to anybody that was in this list. But some patients didn't even read it. Because when we said, "Oh, you would have got the letter", they didn't know what we were talking about. Because we find that at our surgery, that letters don't make much of a difference. We find that if we ring somebody up and talk to them about something or we talk to them face-to-face, that makes more of an impact. So with regards to, I'll give you an example, our flu uptake is 97 per cent…So we don't write to anybody at all. It's done through, when they come to see either myself or the nurse, if it's coming up to flu season we'll say, "Oh, you need to see the nurse at this time". The practice manager is quite good at getting people to come in for things. So that's what we were doing, what we've been doing for HepFREE as well."*
>
> GP, London primary care practice H

Other participants felt that the HepFREE screening invitation letter needed to be tailored to the needs of their local patient population, and should include contact numbers of specific individuals at the practice who could be contacted for more information.

One participant expressed frustration that he had asked the research if the letter could be altered but was advised this would require a protocol amendment to be assessed by the ethics committee for only one individual practice. Another participant mentioned making changes to the letter but did not say if permission from the research team had been sought for this.

> *"We would not send this quality of letter out to our patients normally. [In previous studies] we've been able to comment on letters that went out of the practice and we have made suggestions which have been adopted".*
>
> GP, London primary care practice L

> *"We made a few very tiny changes to the letter. We personalised it…we put the healthcare assistant's name in it. And then we specified who they should contact if they had any problems"*
>
> GP, London primary care practice M

Practices differed in whether they sent patients translated versions of the screening invitation letter in their spoken language, which is likely to have influenced uptake.

Some practices were enthusiastic about opportunistic testing, which the research team were able to facilitate by providing a prompt on the practices' electronic patients records software. Interviewees who had used opportunistic testing for other screening tests said the prompt reminded them to ask eligible patients if they would like to participate, and felt this face-to-face approach worked better in encouraging patients to participate. They also felt it would be easier to offer HepFREE testing if it was bundled with other blood tests the patients required.

> *"For all those people who we were going to invite, we asked Y for the HepFREE people to put an alert on the computer to say that they are eligible for having this. So it makes much more sense if they're in front of you, or you're speaking to them to say, "If we're doing your diabetes, would you also like this blood test?" So I think that's helped."*
>
> GP, London primary care practice F

"I mean most people would require a routine blood test at some point anyway and then we would just ask them whether they wouldn't mind adding an extra one onto it. So that way we could just integrate it into our usual practice really".

GP, London primary care practice M

However, one participant pointed out that their practices would not have the capacity to opportunistically carry out screening for the HepFREE study, because staff would not have the time to go through the consenting procedure with every patient who appeared eligible.

Consenting patients for the study

Concern was voiced by some participants that the consent procedure was too arduous for the patient population as individuals had to provide initials to multiple paragraphs and a final signature at the bottom of the consent form. Problems arose with those patients who did not speak English as a first language and led to longer consultations and a patient who may have placed an X instead of their initials. However the majority of interviewees felt of patients were happy to provide consent once the study had been explained to them, and were comfortable with providing a blood sample for the study.

Two of the interview participants suggested that patients may not fully realise that they are signing up to be part of a study, as the intervention simply consisted of a blood test taken by the practice healthcare assistant or nurse, as per usual, rather than by an external party or research team. As a result it may be more difficult to obtain written consent than verbal consent.

"…if we say, "Look, are you happy to do this? And you sign the blood test to say you're fine to be in the trial". They look a bit perplexed as to why I'm asking them to sign a piece of paper to have a blood test, because you never do that normally for a blood test. So at times I think we might be missing that consent. But verbal consent is certainly there and putting out your arm, and they've turned up with this letter in their hand, saying they want to have a blood test and be part of the study."

GP, London primary care practice F

7.9.2 2017 Interviews

7.9.2.1 Recruitment methods

In 2017, the interviewees were asked to reflect on the recruitment experience, which was ongoing throughout the 18 months screening period at each practice. In anticipation of a large number of responses to the letter, some practices opted to stagger the letter mail-outs. One interviewee felt this was a good way to manage a potentially large number of trial participants.

"Rather than sending them all at once we staggered it, so we would say I don't know, a hundred a month, but rather than sending out the whole lot at once and being inundated"

Specialist Nurse, London, Practice D

Interviewees felt that although some patients responded to the letter, it did not necessarily encourage them to consider testing. Sometimes the response was to enquire why the letter had been sent to them, or what the patient information leaflet meant.

"A few came in with the letter asking "What does this mean?", so yeah the letters had a response".

Practice Nurse, London, Practice B

"There was quite a lot of information for them to take in. Now if we'd sent out a letter saying they need a blood test for this, we'd have got a phone call and they'd have booked in straight away. So from a patient's perspective I think it was too much information for them."

Healthcare Assistant, Bradford, Practice A.

If patients did not respond to an initial letter, some practices opted to send out the letter invitation a second time. Others preferred to use a text invitation, or to phone patients directly. Due to a HepFREE screening prompt on the GP electronic patient records, eligible patients were also offered opportunistic screening if they attended the practice for another reason. Interviewees were asked about their perception of the success of each of these methods in recruiting patients. Some felt that literacy may limit understanding of a letter invitation, or that patients may ignore letters, and therefore opportunistic screening would be a better recruitment method for those patients who did not respond to letter invitation.

“(Patients responded to) opportunistic testing, because a lot of them do not speak English very well, so they don't understand the letters."

Healthcare Assistant, Bradford, Practice A.

"I don't think the letter worked because all we did was batch and print the letter. I think where they'd come in for something else, and we'd spoken to them, that's what made more of a difference."

Lead GP, London, Practice B

"We did it opportunistically. We have an alert on the computer and it says “Patient eligible for HepFREE study”. So at the end of my consultation with them, I would ask them about it. The prompts were for people that ignore letters, they don't do letters. Either they can't read it, or they can't be bothered."

Specialist Nurse, London, Practice C

In contrast, telephone and text reminders were not felt to be a good way of inviting patients to participate in a study, with only one of the represented practices using text reminders, and one other practice using a telephone reminder.

“With such a huge list of eligible patients it would have been difficult to arrange phone calls."

Practice Manager, London, Practice F

Some of the interviewees felt that although the practice offered tests for viral hepatitis prior to the HepFREE study, this trial increased the awareness amongst the local patient population, noting that some patients had asked to be tested due a relative or friend telling them about the trial.

“Patients have spoken to one another and then actually come in and asked for the test”.

Lead GP, London, Primary Care Practice B

The electronic prompt on patient records was helpful in reminding clinical staff of patients’ eligibility for the study

"Our role was to look at the alert, and encourage patients to go for the screen."

Lead GP, London, Practice E

7.9.2.2 Process of Recruitment

During the recruitment process, primary care teams were encouraged to liaise with the HepFREE Trial team for any support required in delivering the intervention. This included administrative issues in sending out letter and texts in order to invite patients for testing, referring positive viral hepatitis outcomes to the HepFREE team for a secondary care appointment, and additional IT and phlebotomy support if required. Interviewees were asked to comment on their communication with the Trial team regarding recruitment and follow-up for patients who tested positive for viral hepatitis.

At some practices, a data quality manager facilitated the referral to the HepFREE team. At others, the practice manager was tasked with ensuring the administration of the referral process was completed in a timely fashion. One practice manager noted that the IT support from the research team helped to modify the HepFREE trial search so that positive patients were not identified, which made her daily duties more efficient:

"(The trial manager) showed me something on the computer to tweak the search. That made my job a lot easier."

Practice Manager, London, Practice F

The three GPs interviewed all commented that they appreciated confirmation of a referral (including date and time of appointment) when it was made.

"I would generate a referral on the EMIS system and I emailed it across … and I got a response back to say we've got your referral. I think that's one of the things that's useful, just an email back to say that we've got your referral and the patient is booked in on this date. The reason why it was useful was that then I can make sure that the patient went to that appointment, if I know when it is. Because you'd given us a pre-populated… like a template we could use that we could populate ourselves, the referrals process was very easy. "

Lead GP, London, Practice E

7.9.2.3 Consenting Patients for Recruitment

As part of the ethical approval for the HepFREE trial, patients were required to provide written consent as part of the recruitment process. This involved a healthcare professional explaining the trial, the reasons that an individual patient was eligible for recruitment, the process of providing a

blood sample for testing and how results would be delivered, as well referral for further assessment at the local hospital if the test result was positive.

If the patient was agreeable to participation, they were required to provide initials and signature to a written consent form outlining the above.

Although most of the practices had reported previous research experience, for individual staff members, consenting was a new process.

"At first it seemed very long, it was new to us. So, because (the HepFREE research fellow) was very informative with us, we wanted to be making sure they (patients) understood it all. So yeah, first week it seemed like it takes ages, after that it was very quick."

HCA, Bradford, Practice A

At other practices, staff were more comfortable with consenting patients and one nurse and one GP both described the process as "straightforward". Having written information in patient's own languages was highlighted as allowing a smooth consenting process.

"The patients were given the information leaflet to read and where it was in different languages, that was the best thing about this study. All of the documentation was available in different languages, I think that was a really big deal, because patients were able to read things for themselves."

GP, London, Practice B

Although staff generally found the consenting process straightforward, they did note a small number of patient declined at this stage. Interviewees perceived that the reasons for declining were (i) language barrier, (ii) poor understanding of the study, (iii) paperwork created a more formal approach and therefore patients declined to provide a signature.

The majority of patients were not put off by having a blood test as part of the study, and some GPs felt that patients were encouraged by the fact of having a blood test as part of the study.

"Patients were quite happy to have the blood test and thought it was very valuable. Some patients like screening. You either get a group of patients who don't like to be screened, who don't want to know about their health. And then you've got the other group of patients who are really proactive, who want every test you can offer them."

Specialist Nurse, London, Practice D

"Patients from Asian-type countries, they like to have a blood test! The fact it was a blood test wasn't an issue. Some patients didn't go to do the blood test, I don't think that they didn't go because it was a blood test, I think they've not gone because they just did not have time to go."

GP, London, Practice B

"Here people like a blood test, they don't mind. That's what I sold. "You will get a blood test and it will either be a positive or a negative. Hopefully it will be negative. We assume it will be negative. However, if it's positive there are things we can do." So I think that they did not mind a blood test."

GP, London, Practice C.

Across the 2014 and 2017 responses, it is notable there is a lot of similar themes emerging. One aspect was that the letter may not have encouraged patients to test, either being ignored or not fully understood, and including too much information. Opportunistic screening was again highlighted as a preferred method of recruitment, whereas texts and telephone calls were felt to be too laborious for staff. Support from the HepFREE team and confirmation of receipt of referrals were also highlighted as being important aspects of the research team's input for practice staff.

7.10 Theme 5 Perceptions of Benefits and Outcomes

This topic was only covered in the 2017 interviews. Practice staff members were asked about their perception of the outcome of the trial at their practice.

Staff from high-performing practices recognised that their practice recruited patients throughout the trial period and as a result some patients were newly diagnosed with viral hepatitis.

"I think we participated well as a practice, and I think our patients were quite engaged, and we were able to engage the patients very well. (We were able to) let them know what Hepatitis is"

GP, London, Practice B

"It was one of the ones where we could really see the benefits of doing it, because we were detecting patients who had Hepatitis B or C"

Specialist Nurse, London, Practice D

One interviewee from an intermediate performing practice perceived their recruitment to be good, reporting many patients attending for screening, in response to over 2,500 invitation letters. At a lower performing practice, the lead GP felt that the practice's low involvement in the study was due to other priorities.

"(Practice) participation was pretty minimal really. GPs have so many things to juggle from HIV to diabetes to depression, there's always something we need to be thinking about with every patient. So I don't think it's had any long term benefit".

GP, London, Practice E

When HCPs were asked of their opinion on the benefits of screening study to patients, responses were mixed and may have reflected the practice's outcomes.

"(That's) hard to measure. Because we're in a high prevalence area, (viral hepatitis) is on our minds anyway."

GP, London, Practice E

Other HCPs felt there was material benefit to those individuals who tested positive as part of the study:

"I think this was a study that benefitted the practice, and the patients and the general population in the area. Patients that we screened as positive, if it wasn't for the study, they wouldn't have been picked up... (such as) Asian housewives that have only had one partner, no high risk activity, no operations, had been here for 20 plus years, no reason for us to test them for hepatitis"

GP, London, Practice B

"I think it's really beneficial, obviously hepatitis is serious isn't it? Any study that picks up a condition that is probably going to impact a person's life later on is really important".

Specialist Nurse, London, Practice D

Other interviewees commented that this study was an opportunity to not only test for viral hepatitis, but also to educate the local migrant population about liver health.

"Educating them about … another problem that can occur later on in life."

Practice Nurse, London, Practice C

"We have a lot of South Asian patients, people from Pakistan. I think that in certain areas of where we live and for this population here…we should screen."

Healthcare Assistant, Bradford, Practice A

The practices were updated on their recruitment numbers on a monthly basis during the HepFREE trial. Interviewees reflected on the perceived benefits to practice staff as the results emerged, and at the end of the trial.

"Since doing the study I think about it (testing) more than I used to. So if I'm doing sexual health screening, doing a blood test for HIV, I'll ask them, the patients, about hepatitis b and c as well".

Specialist Nurse, London, Practice D

"And I think it's… sort of normalising it – it's an infection that's out there, it can treated, it can be managed and it's not something you need to be asking for testing for in secret or be ashamed to ask for."

GP, London, Practice B

"For us it was more work! It was good to interact with the patients, find out a bit more about their family life, where their parents are from. For the nurse to get a bit more understanding of the patient and where they come from. But it was extra work."

Nurse, London, Practice C

"I'm from a Bengali background, so it made me think "Oh my Mum could be one as well", so I encourage patients that way. So it's taught me on a personal level."

Receptionist, London, Practice C

Some of the GPs however did not feel the trial would have a long-term impact on primary care screening, or that the trial provided a new testing approach for their patients.

"We're already screening for viral hepatitis. Are we opportunistically screening every Asian, first generation in the practice? No. And that's because we're told how much money it costs to do blood tests and to try and reduce that, and we've been saying "Don't do LFTs, do ALT". "

GP, London, Practice C

"The study was fine. There was nothing special about it. It was just another study that we participated in."

GP, London, Practice E.

7.11 Theme 6 Perceptions of challenges

This topic was only covered in the 2017 interviews. Interviewees were asked about their views on the challenges of recruiting to a screening study in primary care, and of providing viral hepatitis screening for migrant patients registered to their practice. Healthcare Providers were asked about the level of staff involvement because of the research trial at the practice. All interviewees reported that local staff were involved in the study – at one practice a medical student was also a member of the research team.

"All the clinical team were involved. Healthcare assistant saw patients. Practice manager sent out invites, HCA did consent and blood test."

Practice Manager, London, Practice F

Participation was pretty minimal. The manager and the data person did the searches and liaised with GPs when the results came back."

GP, London, Practice E

"Medical student would do the consent, explain to patient what it was, do the blood test, fill out the template. The results went to the doctor…if there was a problem he would come to me… I did most of the follow-up."

Specialist Nurse, London, Practice D

Increased demands on time were highlighted as one aspect of the trial experience that could have been improved for clinical staff, although at the same practice administrative staff were able to balance the research workload with their usual duties.

"It could have gone better if we had the time to implement it, because most of the patients we saw didn't come for that appointment, they came for other things."

Practice Nurse, London, Practice C

"From my side it went well, because I have the time to do it. I had time to call up each patient and explain to them and everyone in reception was supporting as well. They were doing their own thing, looking at the alerts as well."

Receptionist, London, Practice C

One GP interviewee from a high-performing practice was very positive about the experience of being involved in the trial.

"I think it's something that should be part of a national programme because it's raising awareness and I think it's reducing rates of certain diseases. I think that the hepatitis screening should be made as part of your standard health check and the GP practice is the ideal place to do it."

7.12 Discussion

This qualitative study of healthcare professionals' opinion on testing for viral hepatitis in primary care across two timepoints gives us a unique insight into the challenges in providing this type of screening in GP practices. Over the course of these interviews across three years, pre and post screening at intervention practices, healthcare professionals have been able to share their experiences of engaging patients in a clinical trial, their understanding of viral hepatitis, and their opinions on the barriers and facilitators to testing in this setting.

Several key themes linked into what Primary Care services need to provide viral hepatitis screening – financial incentive, appropriate skillset and numbers of staff, and provision of training. Across both sets of interviews, HCPs alluded to the challenges in providing screening with limited resources and time.

The main HepFREE screening outcomes showed that incentivising practices financially leads to higher uptake than practices in the control arm, but even within the intervention arm there was considerable variation in uptake. Recruitment of patients was challenging for practices, despite the perception of staff from the intermediate or lower performing practices that they had performed well. Essentially their perception was within a vacuum as the staff had no insight into the recruitment outcomes for any other practice in the study. Financial incentives may help practices identify ways in which their particular service can be more successful at recruiting patients for a viral hepatitis blood test.

One key aspect of the post-trial interviews is that a wide range of staff were involved in delivering screening, and all the practices required the involvement of dedicated healthcare assistants as well as admin staff. Some participants felt their practice was hampered without a data manger, underlining the importance of good information governance and IT support for a large scale intervention such as this. The role of the HealthCare Assistant can often been overlooked in Primary Care, but at several practices they were key member of the research team – responsible for recurring and consenting patients as well venepuncture and sample collection.

Additional staff resources would undoubtedly help many of the services we interviewed, but for this particular patient population, an interpreter (or a staff member with the appropriate language skills) was a real boon to the recruitment and consenting process, making the trial accessible to the key population of first generation migrant.

There was little enthusiasm for the invitation letter as a method of recruitment either before or after the screening period, with most practitioners stating that they preferred an opportunistic approach, prompted by an electronic records alert. The simple, cheap and straightforward intervention of identifying at risk patients and setting an electronic alert for their blood test was a familiar aspect of care for clinicians.

One potential barrier to recruitment in the HepFREE trial which would not be present in real life screening was written consent. Small numbers of patients were reported as declining the consent process due to language barriers and poor understanding of the trial. This data was not collected as part of the trial dataset but may have been a factor in poor recruitment in some practices without interpreter facilities on site.

Interestingly, opinions were mixed on the benefits of screening, indicating that even after training sessions and an extended period of incentivised screening, many primary care practitioners do not perceive screening to be beneficial for their local population, although several noted benefits to individual patients.

The main limitations of this study were the limited responses to call for interview participants, even after the offer of £50 incentive. There may have been an element of "HepFREE fatigue" across the 14 invited GP practices. All of them had been involved with the HepFREE study over a three year basis this point and staff had had multiple contact with the HepFREE research team. They may have felt their contribution to the study was at end after data collection and closure. Also, the interviews were recorded between 1-2 years after the trial had concluded at the practices, and in some cases recall of experiences may have been affected by the passage of time.

The HepFREE provider study shows that the voices of primary care clinicians and healthcare professional should play an important role in the shaping of future viral hepatitis case-finding programmes at both national and local level. GPs have a key insight into the ability for their services to provide the service delivery needed to test migrant populations in their care, and any additional workload for primary care should be attached to a financial incentive and / or the provision of additional staffing in order to provide a wide coverage for future viral hepatitis screening programmes.

8. DISCUSSION

8.1 Introduction

The HepFREE trial was developed to determine the feasibility of testing migrant populations for viral hepatitis in primary care and to determine the best location of follow-up for those testing positive for HBV or HCV infection.

My role in the trial was as Clinical Research Fellow for the East London and South London sites. I was also trial manager for the trial in its latter two years.

I have presented the data analysis of the whole HepFREE trial which I collaborated on with the HepFREE statistics team. I have also presented my own analysis of other HepFREE data outcomes for disease staging, community vs standard follow-up clinics, pre-trial surveys of eligible patients and their subsequent testing uptake, and qualitative interviews of healthcare professionals delivering testing.

In this chapter I will summarise the findings of the HepFREE trial and associated sub-studies and discuss how this adds to our current knowledge of viral hepatitis testing strategies. I will explore what the research findings tell us about barriers and facilitators to screening for viral hepatitis in the migrant population.

I will also discuss how the HepFREE outcomes can inform future plans to achieve the WHO goal of viral hepatitis elimination by 2030 (1).

The objectives of my research were:

1. To determine the screening rate at practices where GPs are supported and incentivised to screen migrants for viral hepatitis, compared to standard screening rates

and through my own sub study analysis

2. To determine the range of disease staging of those testing positive for viral hepatitis in primary care
3. To determine if community-based follow-up and management is superior to standard hospital-based follow-up
4. To analyse the outcomes of the pre-trial survey of eligible patients on their understanding and knowledge of viral hepatitis, and if this influenced their attendance for screening
5. to explore the views and opinions of healthcare professionals on their experience in delivering the HepFREE trial.

8.2 Outcomes of the HepFREE Trial

Previous studies and modelling data have suggested that screening immigrants for viral hepatitis is both clinically effective as well as cost-effective (114)(86)(43). However these studies were performed on a small scale in local populations with well-motivated clinicians. Similarly sized studies have also shown that (between 40-75 %) of patients would be referred for therapy(5). This evidence prompted the UK National Institute for Health and Care Excellence NICE) to issue guidance in 2012 recommending the testing of migrant patients for viral hepatitis in primary care settings (3). However the uptake of this guidance has not been tested in the UK. HepFREE was the first national, large scale randomised control trial to assess primary care testing rates of migrants in the UK.

8.3 AIM 1: To determine the screening rate at practices where GPs are supported and incentivised to screen migrants for viral hepatitis, compared to standard screening rates

8.3.1 The HepFREE Screening Trial

HepFREE was a large-scale randomised control cluster trial designed to measure the frequency of viral hepatitis testing in primary care in England and compare this to the uptake from the intervention of incentivising GPs to invite patients to test. Other outcomes looked at the current prevalence of viral hepatitis in immigrants and outcomes in a secondary trial of comparing attendance at follow-up standard of care hospital setting versus follow-up in a community based service.

Overall testing uptake was 1% in control practices (where only educational updates were provided) and 19.5% in interventional practices (funding and support provided), indicating that incentivising GPs with financial rewards and providing additional resources can make a considerable impact on testing rates. Indeed, without such incentives, the national guidance(3) for viral hepatitis screening is not adhered to. However even with incentives testing rates were lower than testing projections (estimating 40% of the population would be tested).

This uptake is a new finding which has not been previously determined for this population in primary care.

People from Pakistan were more likely to attend for testing, perhaps reflecting engagement of general practitioners based in high density areas with such patients (especially Bradford) but across all the sites, testing of patients from other ethnicities was poor. Older patients (age > 40 years) were also more likely to agree to testing, perhaps reflecting their higher attendance at primary care.

Prevalence rates for both HBV and HCV were around 1%, however viraemic HCV was 0.3%. This is lower than previous estimates for HCV(174) in the migrant population in the UK and in relation to previous prevalence studies listed in Table 3, the prevalence rates in the HepFREE trial sit at the lower end of the scale for both HBsAg and HCV RNA. This is a new finding for migrant populations in the UK and would suggest that in this country the overall viral hepatitis burden amongst immigrants is lower than expected. However, there is higher prevalence in particular sub-groups, such as patients from Pakistan. Despite the lower than anticipated prevalence, these values still justify screening in the UK migrant population with the advent of the new cost-effective DAA therapies. Of note the HepFREE prevalence rates were most similar to those found in screening migrant patients with tuberculosis (99), suggesting that a combined infectious disease screening of targeted migrant populations could be time-efficient as well as cost-effective.

8.3.2 Invitation Letter

The HepFREE trial also tested the use of a bespoke invitation letter (including details of viral hepatitis, risks of hepatocellular carcinoma and reasons for the invite) versus a standard invitation letter. This was the first (to my knowledge) large-scale randomised trial of specifically tailored invitation letters in a primary care setting. An enhanced letter did not encourage of uptake of testing compared to a standard letter (3.7% vs 4.5% response within 31 days), and of note the invitation letter overall had a poor response from invitees. As providing an enhanced letter was a costly intervention, it is not a recommended approach in inviting eligible patients.

8.3.3 HepFREE Community vs Standard Follow-up Trial

The HepFREE trial design included an embedded study of community treatment vs standard treatment, to my knowledge the first such study of viral hepatitis management for migrant populations.

However setting up community clinics in busy GP practices proved to be more challenging than originally anticipated, with logistical problems such as room availability, local agreement with GPs and transport of expensive DAA therapy from secondary care centres delaying the initiation of this part of the trial.

Patients who were allocated via cluster randomisation to the community care arm and asked to wait until treatment could be arranged in their local centre were either not willing to delay therapy and management or would not consent to community therapy. Along with the incremental availability

of new DAA therapy for treatment of HCV during the HepFREE trial, these difficulties prevented the completion of a fully powered study.

However the outcomes of the adherence to medical advice and therapy in the immigrant population screened in primary care were excellent, whether attending hospital or community based clinics.

Although this sub study was statistically underpowered, the data suggests engagement with hospital based clinics (85.4% attendance) was excellent and there are very unlikely to be any benefits to offering community based clinics instead (81.1% attendance). Given the extra costs, staffing and logistical arrangements required to provide community clinics it cannot be recommended for immigrant patients with HBV or HCV infection.
Community based therapy would be better targeted at other populations at risk of viral hepatitis such as people who inject drugs(175).

8.3.4 Strengths and Limitations of the HepFREE Trial

The strengths of the HepFREE trial were the large study population (a total of 90,250 eligible patients across control and interventional practices) and the large number of GP practices involved in recruitment at Bradford, East London, South and Oxfordshire (for the low prevalence study, data not reported in this thesis). The use of cluster randomisation also provides benefits such as increased administrative efficiency for a population of this size, and reduced risk of experimental contamination (with practices being randomised to either interventional screening or control, or standard or enhanced invitation letters)(176).

The very low testing rates in control practices was an unexpected finding and reduced value of the power calculation for the trial. However, this did provide a very clear signal that testing for viral hepatitis in primary care without financial incentives occurs at background levels, and the provision of funding and support for GPs should be costed into any elimination programme for viral hepatitis.

8.4 AIM 2: To determine the range of disease staging of those testing positive for viral hepatitis in primary care

The HepFREE trial found a positivity rate of 1.06% for HBsAg and 0.93% for HCV Ab (0.3% were viraemic) in a population of 11,929 tested patients from 58,512 eligible migrants living in Bradford and London. Of the 220 positive patients, 128 engaged in diagnostic and imaging assessments.

The 220 positive patients were all identified as part of HepFREE invitation to testing, and therefore had not been offered testing based on abnormal liver function tests or clinical evidence of liver disease. It is reasonable to infer that these patients were asymptomatic and may not have been otherwise tested by their GPs for viral hepatitis.

Of the 128 patients who engaged in diagnostic and imaging assessments, 13 (10.1%) were found to have severe fibrosis or cirrhosis, putting them at increased risk of hepatocellular carcinoma. An additional 7 (5.5%) were either HDV co-infected or HBeAg positive, also putting them at increased risk of HCC. These are notable findings and underline that the migrant population is at risk of developing asymptomatic severe liver disease due to undiagnosed viral hepatitis infection. Other studies have recognised the trend in increased risk of liver disease in this population due to viral hepatitis infection (90,177,178), but this is the first time an asymptomatic population has been diagnosed via a primary care testing program.

Since control practices had very low testing rates, asymptomatic viral hepatitis infection may be a considerable barrier to testing in primary care, as has been noted in previous research (115).

Prevalence of viraemic HCV infection (0.3%) was lower than expected(2) and skewed towards the under 50 years age group, a factor future testing strategies should take into consideration, particularly as testing and curing younger patients will have impactful QALYs.

Engagement with diagnostic and imaging appointments in the positive population was high, perhaps indicating that this is a health-aware group who have already responded to the invitation to testing and therefore are more likely to follow-up on the result. These results should be contrasted to the outcomes of opt-out testing engagement outcomes (40,100) which are typically lower in opportunistic testing environments.

8.5 AIM 3: To determine if community-based follow-up and management is superior to standard hospital-based follow-up

128 patients who attended their diagnostic and imaging appointments were eligible for randomisation for follow-up in the HepFREE follow-up trial. The 38 patients who tested positive in London were analysed in my substudy. 16 were randomised to community care with 22 followed up in standard (hospital) setting.

The data shows that there is no significant difference in engagement between the standard care (85.4% attending) and community care (81.1%) arms of the follow-up trial.

One of the strengths of the study was the opportunity to follow these groups through from testing to diagnosis to staging to treatment and management. The longitudinal nature of this data gives a good indication that patient engagement continues beyond the initial diagnosis and that patients referred from primary care will remain engaged in follow-up long-term if appropriate.

The excellent engagement rates in the HepFREE trial are in stark contrast to previous findings of undertreatment and poor engagement in migrant populations (79–83) where underdiagnosis was felt to be an important contributor. From the HepFREE outcomes, I would argue that we are seeing the ongoing engagement of a health-conscious group of patients: those who have already agreed to be tested will continue to engage if they are diagnosed positive and are aware that treatment and management is available.

The main limitation of this analysis is the small numbers of patients who consented to randomisation and were seen in the community care arm (16 patients). Even with this relatively small number, arranging community-based care proved to be a logistical challenge. It should also be noted that during 2015-2017 the new DAA therapies were available incrementally on the NHS and therefore some patients opted to pursue therapy with interferon (the only available option for HCV Genotype 3 during 2015 and most of 2016) or wait until DAAs were available. Fortunately, since 2018 all people diagnosed with Hepatitis C can now access DAA therapy via the NHS.

This is the first such randomised control trial for standard vs community therapy for immigrant patients. Other trials have found good outcomes for community based therapies for PWIDs, but none have previously investigated their role for immigrant patients (179,180).

From the overall outcomes of the follow-up trial, the data suggests that community-based care is of no benefit to this population, and with the difficulty in setting up such a service, would be wasteful of valuable staffing and time resources.

8.6 AIM 4: To analyse the outcomes of the pre-trial survey of eligible patients on their understanding and knowledge of viral hepatitis, and if this influenced their attendance for screening

Previous analysis of the knowledge of immigrants regarding viral hepatitis showed that awareness of viral hepatitis and its causes and sequalae was poor (131). This was supported by qualitative interviews with GPs and key informants around knowledge amongst at risk immigrant communities(132).

These qualitative studies examined background knowledge of viral hepatitis in immigrant communities and found considerable misinformation about these conditions with confusion about symptoms and modes of transmission.

I analysed the responses of 370 participants eligible for HepFREE screening in pre-screening surveys of their knowledge and understanding of viral hepatitis. In this analysis I was particularly interested in understanding if any demographic or knowledge parameters indicated an increased likelihood to test.

Most striking was the similarity of uptake in this group of 370 eligible patients compared with the 58,000 invited patients in the intervention arm (24.9% and 19.5% respectively). There were also similarities in age groups (32.4%, 27.8% in age >40 years group) and particularly in ethnicities (31.7% and 32.5% for Pakistani population, 9% and 11.7% in African populations).

Other indicators of likelihood to attend for testing were knowledge of treatments and having a friend or family member treated for viral hepatitis. These were statistically significant and may have been driven by a better awareness of viral hepatitis amongst the Pakistani population. However, it is important to note that positivity rates for viral hepatitis are similar amongst Pakistani (2.0%) and African populations (1.7%) and so more should be done to improve understanding of viral hepatitis risks in the African population. Mood and illness perceptions did not have an impact on screening uptake.

A strength of this study was that the population was representative of the final screened population, with male/female, <40 years and >40 years and Pakistani and African patients well matched. However, the African population was made up of individuals originally from a wide spread of territories from across the continent and it is not clear if certain African states or cultures are better informed regarding viral hepatitis than others.

There is limited similar data on the predictors for testing in migrant populations. Previous studies highlighted a lack of information on disease and stigmatisation, as well as language being an

additional barrier to testing (79). One qualitative study in the US found that predictors for African Americans to attend for testing included having a blood transfusion prior to 1992, perceptions of benefits, severity, and subjective norms (181).

Information campaigns focussing on new hepatitis treatments and the potential risks of undiagnosed infection should be targeted at the African community to increase testing rates in this population. Such campaigns could be part of a wider drive to educate at-risk populations on the commoner causes of liver disease, such as alcohol misuse and metabolic syndrome.

Previous studies(132) have suggested that low viral hepatitis screening rates may be due to focus on employment and limited access to healthcare professionals who can speak the same language.

Therefore testing campaigns should be led by community advocates who speak appropriate languages. Testing should be made available out of working hours to improve uptake rates in this population.

8.7 AIM 5: To explore the views and opinions of healthcare professionals on their experience in delivering the HepFREE trial.

My qualitative study sought the opinions of healthcare professionals on delivering a viral hepatitis screening program in primary care.

Several key themes emerged from these interviews – that GPs require IT and staffing support to deliver hepatitis testing, and financial incentives motivate the practice to achieve targets. Perception of outcome can be different to the reality, and so comparison with other local testing centres may be helpful in supporting underperforming sites.

For those providing training to primary care it is important to include all staff groups in training, and to identify a testing champion. At various HepFREE practices this was as likely to have been a practice manager, healthcare assistant, or specialist nurse as well as a GP.

The importance of an interpreter was also highlighted as a key concern for primary care staff, in order to make screening more accessible to first generation migrants.

Most HCPs preferred text or electronic prompt to the invitation letter which garnered little enthusiasm.

Training sessions should also focus on the benefits of screening, prevention of chronic liver disease and HCC and the curative rates of the new DAA drugs. There were mixed opinions on the benefits of screening and it may be that HCPs need persuading that their local population can benefit.

The strength of this study was the semi-structured interview across two time-points which gives a strong sense of how the trial delivery was viewed at the beginning and end of the testing period.

The main limitation of the study was the poor response to the call for interviewees, with eight participants at the end of the trial, compared to twenty before the trial was fully implemented. GPs. This meant that very few of the original participants were interviewed at the start and end of the trial to give a true longitudinal view of the provider experience.

Previous data has suggested that testing outcomes, referral pathways and patient education are all more likely to be successful when the GP voice is part of strategy planning for viral hepatitis testing (121,182,183), and this qualitative study supports those findings.

8.8 Future Research and Investigation

The HepFREE Trial and its associated substudies show there is still some considerable work to be done to achieve viral hepatitis elimination in migrant populations by 2030. From the findings, I would not recommend there is further research into offering this population community based treatment centres. This would be time-consuming and wasteful of resources. However we still have much to learn about strategies for case-finding eligible immigrant patients from their GP records. The use of electronic record searches will be crucial in processing a large amount of data in ne efficient and timely way. Missing data on electronic records will be a barrier to finding patients and more work should be done to understand why key demographic parameters such as country of birth and ethnicity may be absent in primary care records.

The testing rate increase seen in HepFREE intervention practices compared to standard practices was 1850%, a vast improvement compared with the 60% increase seen in a previous interventional study in Australia. (122) However, as in the Australian study, rates amongst Asian and African immigrant patients could be higher. Future studies should focus on ways of improving primary care testing rates in these populations (perhaps by increasing GP training, engaging community leaders and offering more education to at-risk populations) rather than care delivery. Enthusiastic GP champions and peer navigators could be a source of local knowledge and support for both healthcare professionals and patients and it would be valuable to measure their impact on testing rates.

We did not investigate the role of patient incentivisation for viral hepatitis testing, but other studies have looked at the role of financial compensation and travel stipends to encourage testing and engagement in at-risk populations, particularly PWIDs (184,185). However, this has not been specifically studied in migrant populations, and it would be worthy of further investigation, perhaps in the context of other interventions aimed to improve testing rates. From the results of our pre-screening survey I would argue that engaging peer support workers for screening programmes may be more effective than financial incentives for a population where improved knowledge of viral hepatitis and those affected has an impact on testing uptake. In the HepFREE trial, patients who tested positive went on to engage well in follow-up at both community and standard care settings, and I conclude that this population do not require further intervention to support ongoing engagement

It would be valuable to do more work with healthcare professionals to understand the drivers behind offers of viral hepatitis testing, particularly in opt-in settings. Conversations between clinicians and patients may be framed by unconscious bias, and I expect that this played a role in which patients were offered testing at our GP practices. Fitzgerald and Hurst (186) highlighted the dangers of implicit bias in healthcare which may lead to disparities, and healthcare research carries its own cycle of bias (187). Unconscious bias of the healthcare professionals within a large real-world cluster-randomised trial such as HepFREE may have led to some patients not being offered testing as that process also involved providing written consent. GPs I interviewed felt that some patients were actively seeking blood tests and would be agreeable to testing, whereas other healthcare professionals judged the information sheets and consent process to be challenging for patients. The opportunity to explore this through unconscious bias training may help individuals reflect upon their own affinity and conformity biases, as well as understanding institutional bias that can impact on larger healthcare models.

8.9 Summary

The HepFREE trial data shows that to improve viral hepatitis screening rates in primary care, GPs need to be incentivised and should also be offered training and staffing support. Such interventions are clinically effective and cost-effective. The target population has a prevalence of around 1% for HBV and 0.3% for viraemic HCV, which is lower than expected. However, they are at risk of developing asymptomatic severe liver fibrosis or cirrhosis and may not be tested in primary care without invitation.

Barriers to testing uptake include poor knowledge in the target population (particularly regarding the new HCV treatments), limited resources in primary care, and lack of priority for viral hepatitis testing amongst both the target population and primary care HCPs. HCPs should be educated on the risks of asymptomatic, undiagnosed viral hepatitis.

Facilitators to testing include a testing champion and training resource at primary care practices, financial incentivisation and knowledge of peers who have been treated amongst the target population.

Other models of primary care screening for HCV in the US used similar support mechanisms for GP practices, including Healthcare assistant-initiated testing, reflex laboratory-based HCV tests, and electronic health record modifications to prompt, track, and facilitate reimbursement for tests performed(115). Future elimination strategies should consider implementing these tools.

Community based care is of no benefit to the migrant population, although it has been shown to be successful for other high risk groups. In the interests of cost-saving it should not be implemented for this population.

Given the large scale nature of the HepFREE trial, these findings are applicable to immigrant testing in the UK and around the rest of the globe. However, despite the increase in uptake in the interventional arm, attendance for testing was less than 20%. With the WHO's target to eliminate viral hepatitis by 2030, additional measures will be needed to encourage GPs to roll out testing for immigrants in primary care.

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Appendices

Appendix 1

The HepFREE Trial Protocol Version 9

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:
	Dr Sally Burtles
	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 8.0, dated 18th August 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:

Chief Investigator Site:

Signature and Date:

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 8.0, dated 18th August 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.

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	8.0 dated 18th August 2016
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 58 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
SVR12	Sustained Viral Response 12 weeks after treatment (i.e. virus not detected 12 weeks after treatment for viral hepatitis).
TMG	Trial Management Group
TSC	Trial Steering Committee

Index **Insert 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 maternofetal 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 compliance with clinical management plan 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 (comparison A).
- To determine the screening rate of intervention practices compared to the screening rate in control GP practices (comparison A.)

To determine whether the provision of an enhanced patient information invitation letters increases attendance for testing when compared to standard information invitation letter (comparison B).

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 (comparison C).

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
- To determine the number of eligible patients across the participating GP practices
- To determine the overall level of compliance with diagnostic and prognostic events for all patients that test viral hepatitis positive as part of this trial (overall outcome D).
- To determine the level of compliance with the management plan for patients that test positive for viral hepatitis.
-

Primary outcomes

- In control GP practices, 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). In intervention GP practices: The proportion of patients eligible for this study that are invited to screen (determined by a review of the number of invitation letters sent to eligible immigrants registered at the GP practice at the initiation of the study).
- The proportion of potential participants that attend for testing (for comparisons A & B)
- 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.

- The costs associated with delivering the intervention will be recorded and used for the cost effectiveness analysis.

Secondary outcome

- Proportion of new registrants who agree to undergo testing for viral hepatitis. Patients who are newly registered with the practice during the study period and who are eligible for screening will be offered screening if they attend a practice with 'unrestricted' testing or one of the control practices. Rates of testing in 'new registrants' will be reported along with compliance with treatment outcomes.

- The proportion of viral hepatitis positive participants that comply with the clinical diagnostic and prognostic assessment in secondary care. Engagement with diagnostic and prognostic assessment is defined as completion of three diagnostic and prognostic events (including diagnostic assessment visit, a Fibroscan® and/or ultrasound and a statement of clinical management plan from the hepatology team). The schedule of these events will be dictated by local policy. For patients who are HCV antibody positive but HCV RNA negative attending the GP practice or the local hospital on two separate occasions will be deemed as compliance with diagnostic and prognostic assessments(for overall outcome D)
- The proportion of patients that are compliant with their prescribed clinical management plan in the different treatment arms (community care Vs Standard hospital care). Compliance with the clinical management plan is defined as:
    - Attending at least 1 visit after the management plan has been agreed by the participant and the clinicians (for comparison C)

- Patients that test positive for viral hepatitis and are prescribed medication to treat their viral hepatitis will be monitored for their adherence to therapy. Patients will be considered to have adhered to therapy if they successfully complete 80% or more of their prescribed therapy.
- The 'outcome of therapy' will also be monitored. A successful outcome of therapy will be defined as sustained viral response 12 weeks after treatment completion for hepatitis C patients. The definition of successful outcome of therapy for hepatitis B treatment is a reduction in viral load to <80% of starting value within 12 weeks'.

2.2 Trial Design

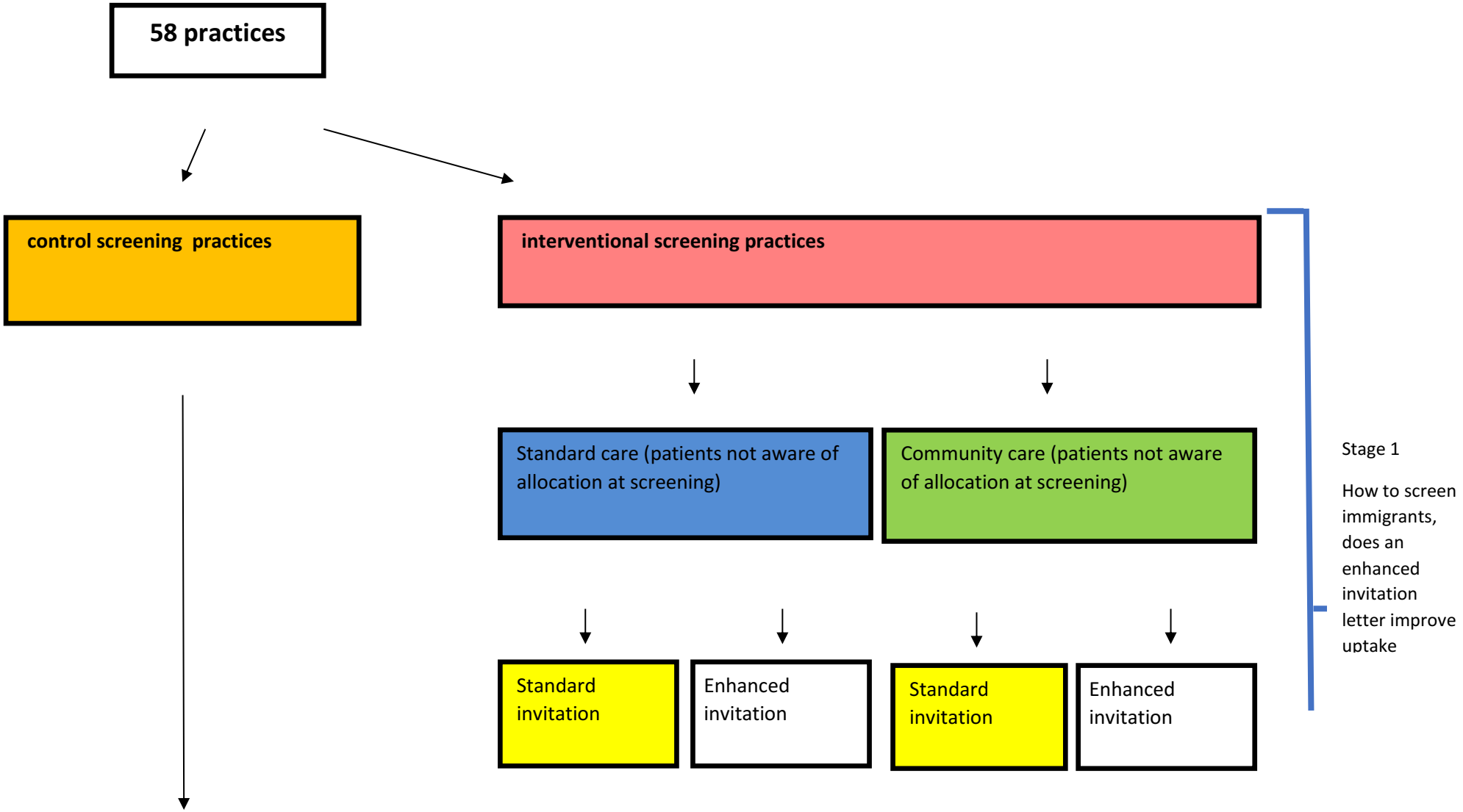
It is a two stage cluster randomised trial. The first stage (two arms) determines how to effectively identify and screen immigrants from 'at risk' ethnic minority communities for chronic viral hepatitis. Within the first stage of the trial we will determine whether or not patients who receive an enhanced patient information invitation letter agree to participate in testing at the same rate as patients who receive a standard patient information invitation letter.

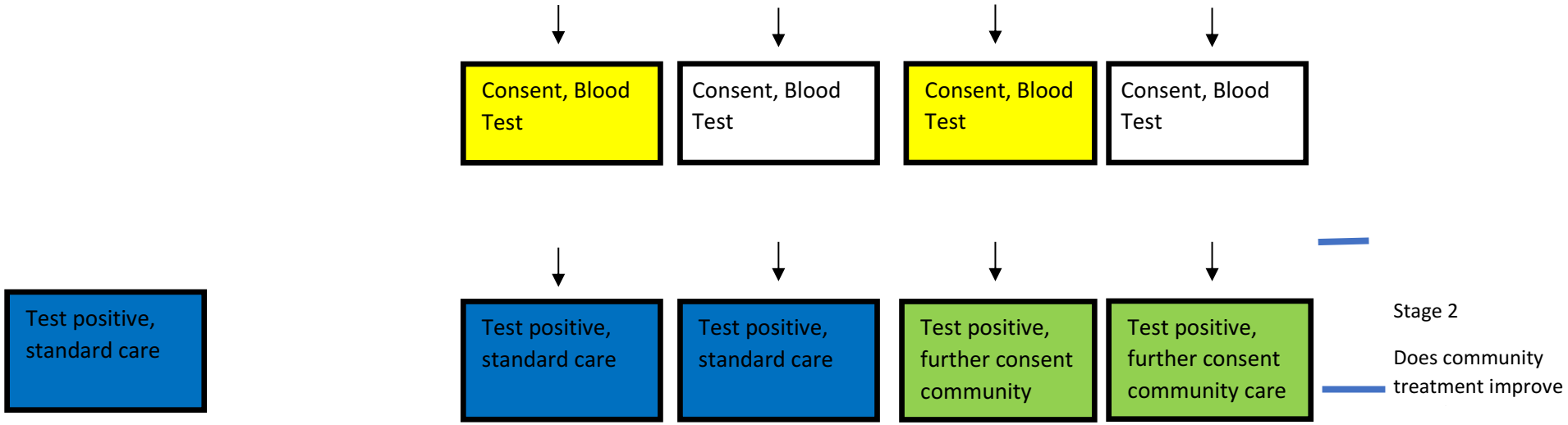
The second stage (two arms) investigates the overall engagement rates for positive patients with diagnostic and prognostic consultations and compliance with their clinical management plan. It also explores if treatment in primary care (community based therapy) impacts on the adherence to therapy.

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

Comparison B: White vs yellow practices

3. Subject Selection

3.1 Number of Subjects and Subject Selection

Pre-screening Component (Survey)

Prior to the commencement of screening, 4 'intervention' GP practices will be involved in the Pre-screening component of this trial. The GP practice will be involved in generating a representative random sample identified by ethnicity group, based on the inclusion criteria specified in section 3.2. The sample will reflect the wider population of those that are potentially eligible for Stage 1 of HepFREE. Up to 3500 of the pool of potential participants will be contacted to take part in the pre-screening survey component.

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.

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.

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 a referral to the local hepatology department to receive appropriate therapy. Once referred, 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)

In the control practices patients will be offered a screening test opportunistically, as per standard of care. There is no intervention at the control GP practices.

Immigrant demographics from control GP practices for a further 4,000 potential participants will be monitored with regards to testing for viral hepatitis, and the total number of viral hepatitis positive

patients will be noted. The total number of positive patients that engage with subsequent care will be noting by looking at the total number of positive patients that have further diagnostic tests. This will be fully anonymised prior to data being exported and sent to the data management team for data collection. Aggregated ethnicity data on patients that fit our inclusion criteria will be provided to the data manager.

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 both GP practices, participants found to be viral hepatitis positive will be referred to their local hospital where they will have the option to start stage 2 of the HepFREE study. In secondary care, participants will have further diagnostic and prognostic consultations to ascertain the severity of their liver disease. Once an appropriate clinical management plan has been agreed between the clinical team and the patient, the patients will then be able to start their prescribed treatment or active monitoring in either their local hospital (standard of care) or in community care. Full details of the consent procedures for this arm of the trial is detailed in section 4.1.3 and details of stage 2 of the trial are listed in section 4.2.

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.

In the intervention practices, it is the responsibility of the investigator, or a person delegated this task by the investigator, to obtain consent for the blood test and written informed consent from each subject to 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.

4.1.3 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. 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 practice's allocation at the time when consent is sought (see section 4.2.4). Participants that consent to take part in stage 2 of the trial, will subsequently be informed of their treatment/monitoring allocation by the doctor or health care practitioner who will manage their treatment/active monitoring. 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). Supplementary consent to remain on the study will be sought at the first visit to secondary care subsequent to a referral. Supplementary consent can be sought at following visits to secondary care only if conditions do not allow for the consent to be sought at the first visit to the local hospital. However, it is a pre-requisite that the consent must be stated (written) prior to the patient adopting their trial allocation (community care Vs Hospital care).

4.2 Study Procedure Overview

Practice selection for invitation to this study will be based on an established patient population of first and second generation immigrants from 'at risk' countries. Following invitations to a larger group of practices we expect 58 GP practices across East London, South London and Bradford to be randomized in this study. 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.(comparison A)

In the second stage trial to assess treatment options we will compare groups B & C with groups D & E(comparison C)

In a supplementary analysis to assess the effect of the enhanced invitation on testing rates we will compare groups B & D with groups C & E (comparison B)

4.2.1 Pre-screening Component (survey)

A small subset of up to 3500 potential participants from up to 4 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.

Data collected from the pre-screening database will be linked, using the pseudonymised identifier generated by the GP database, to screening data collected as part of stage 1 of HepFREE. This is to ascertain whether there are certain beliefs of perceptions about hepatitis that indicate whether a patient is more or less likely to screen for viral hepatitis when offered a screen and therefore answer our primary objective detailed in this protocol. This linkage will not lead to identification of patients.

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 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. Details of the consent process is detailed in section 4.1.2.

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 maximum 18 month 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 are offered a referral to the local specialist hepatology team. All participants that are referred will initially be seen at their local outpatient's hepatology clinic, by the HepFREE Clinical Research Fellow or a delegated clinician, to ascertain their diagnostic and prognostic status which will determine the treatment or level of monitoring that is required. It also ensures that community care, as a potential treatment location, is appropriate for the patient. Supplementary consent is sought from all patients that are referred as part of the HepFREE trial (section 4.1.3). 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. If the participant consents to remain on the study, they will be unblinded to their treatment allocation. Patients who wish to enter stage 2 of HepFREE will receive treatment/monitoring in the specialist out patients clinic in their local hospital or in a local community care practice as 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).

Patients who test positive for viral hepatitis will be monitored for their level of engagement and compliance which will be monitored in two separate ways.

1) Overall engagement with diagnostic and prognostic consultations measured by completion of the following events as three separate entities: i) a diagnostic assessment consultation ii) an ultrasound/ Fibroscan® assessment iii) receipt of a management plan
2) Compliance with the agreed clinical management plan, measured by attending at least one visit after the receipt of a clinical management plan.

These definitions will allow an assessment of engagement in patients who do not wish to receive or are not suitable for antiviral therapy at this time.

Data relating to engagement (outcome D), compliance with management plan (Comparison C) and data relating to the secondary outcome will continue to be monitored until the end of data collection in February 2017 for all patients that screen positive as part of Stage 1 of HepFREE. Due to due to fast developments in treatment availabilities for hepatitis C and change in NHS

policy, with regards to prescribing new hepatitis therapies, the 'clinical management plan' for some patients may change throughout the course of the trial. Continuing to collect outcome data for all HepFREE patients that screen positive until Feb 2017 will enable us to obtain 'adherence to therapy' and 'response to therapy' (secondary outcomes) information for patients whose treatment options change during the trial period.

For patients who are randomised to community care, they will continue to receive their hepatology care, if appropriate, in the community until the HepFREE data collection stops in February 2017. This is to allow the patients enough time to adjust to their treatment regimes in the community before moving their care back to 'standard of care' based at the local hospital once their study visits have been completed.

Adherence to therapy will be analysed as a secondary study outcome. Adherence to therapy will be defined as having taken 80% or more of the prescribed medication as described in section 2.1.

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).

4.2.5 Investigating Barriers to Screening in Primary Care. "The HepFREE Provider Experience" Qualitative Research

This is a qualitative substudy linked to the screening rates in Stage 1 of the HepFREE trial.
Data collected so far from stage 1 of the HepFREE study shows that screening rates differ vastly across different GP practices (from 2%-90%) and the purpose of this substudy is to determine why some GP practices are effective at engaging with patients, and others are not. This will enable the HepFREE team to make future recommendations about key GP practice characteristics that indicate the hepatitis B/C screening intervention would be most effective.
This substudy follows on from previous pre-trial research into the attitudes of primary care healthcare workers towards screening patients for viral hepatitis. (Study approved through the Queen Mary Research Ethics Committee - Ref no: QMREC2012/02). Healthcare workers of various grades were interviewed at 14 GP practices in Bradford, East London and South London between July-October 2014. Since then, all 14 GP practices have participated in the 18 months of "HepFREE" viral hepatitis screening programme.

In this qualitative substudy we will interview a general practitioner, practice nurse, healthcare administrator and/or practice manager at 12-14 practices to assess their attitudes to screening in primary care following completion of the screening programme. All interviewees are adult healthcare workers, and many of them will also have contributed to the pre-trial qualitative research. Written informed consent will be sought from GP practice staff who agree to be interviewed. A participant information sheet will be provided detailing the aims of the interviews. All interviewees will be made aware that participation is voluntary and they can stop the interview, or refuse to answer questions, at any time. If the interviewee was part of the pre-trial

research then they will be asked for permission to link information provided as part of this interview with information provided prior to the HepFREE trial commencing. Interviewees can opt out of this link if they so wish. Participation in the interviews will be kept confidential. The interviewer will not have access to identifiable research material from the pre-trial interviews until the interviewees provide elicit consent for this. As a reimbursement for their time, all interviewees will be offered a shopping voucher to the value of £50.

Interviews will be either face-to-face or by telephone and last approximately 30 minutes and will be conducted between September 2016 – June 2017. All interviews will be audio-recorded and responses will be anonymised. Interviews will be conduct by trial staff who have had no previous direct contact with the primary care practice. No patient data will be used.
Questions will explore specific quantitative data collection such as practice staff to patient ratios, staff to room ratios, patient recruitment levels and the presence of onsite phlebotomy services. Other question will explore motivations and challenges of running a screening programme (perceived benefits to patients and to practice, impact on time and resources, impact of payment and the prioritisation of the study in a busy practice), the practical implications of being involved in a research study (local trial training, use of trial dataset) and the challenges of recruiting and consenting patients to the trial.
The anonymised responses will be collated along with the previous pre-trial responses to assess attitudes before and after the 18 month screening programme and to identify potential barriers to viral hepatitis screening in the primary care setting. With consent, the ethnicity and country of birth of the interviewer will be recorded.

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 will be stratified by region and 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 will receive treatment 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 anti-viral adherence to therapy will be logged at the SVR 12 follow-up visit. Definitions of 'adherence to therapy' and 'outcome of therapy' are detailed in section 2.1.

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 engaged or not with the diagnostic and prognostic consultations.

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. For Control GP practices, the HepFREE team may liaise with local laboratory teams to obtained anonymized screening outcomes of Hepatitis B and C for eligible participants, where this information is not available at GP practices. In this case, any information shared to the HepFREE team will be aggregated and anonymous.

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 56 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, i.e. 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 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).

Qualitative data collected as part of the pre-screening questionnaire will be linked to stage 1 of HepFREE to determine whether there are specific beliefs or perceptions that determine whether a patient is more or less likely to screen for viral hepatitis.

Stage 2:

Main comparison: Overall engagement rates = engagement with diagnostic and prognostic consultations (section 4.2.4). Standard treatment v treatment in community outcome = attendance to at least one visit following the agreement of the clinical management plan. Generalised estimating equations using logit link to account for binary outcome as primary analysis, accounting for region and cluster size.

We will use the intention to treat principle when identifying which clusters and arms to analyse individuals in i.e. based on the allocation of the referring GP practice.

7.4 Cost Effectiveness Analysis

Data collected as part of HepFREE will be used to determine the cost effectiveness of the screening intervention, as per the primary objective (section 2.1).

The economic model that will drive the cost effectiveness analysis will be based on a Markov Model. The main focus will be to determine cost-effectiveness for a range of NHS policy options in hepatitis screening, as well as understand the uncertainty and sensitivities associated with these estimates. Modelling will be associated with the whole study population rather than individual cases although sub-group analysis may require that we can identify key population groups (e.g. ethnic or age related).

7.5 Disease Progression Modelling

The team will use data collected as part of HepFREE on prevalence of hepatitis B and C and disease severity to model the current burden of disease in different local communities. In particular, the team will look at the distribution of fibrosis and cirrhosis in relation to demographic factors like age, gender and ethnicity. This will enable the team to provide an estimate of future impact of hepatitis in order to recommend prioritisation strategies for screening in communities at higher risk of developing viral hepatitis related complications. Data input for this analysis will be based of hepatitis positive patients who gave full informed consent to the HepFREE study.

7.6 Analysis of Barriers to Viral Hepatitis Screening in Primary Care

The team will use descriptive statistics to describe key characteristics of practices with low, medium and high screening rates. A detailed qualitative analysis will be performed on themes arising from the interviews.

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 SystmOne, by a HepFREE specific template. Only authorized personnel will have access to the EMIS/SystmOne 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. Pseudonymised data collected as part of the pre-screen survey will be linked to Stage 1 of HepFREE screening data using a patient ID that does not identify the patient. Consent to collect both datasets is a pre-requisite for collecting both survey data (oral consent) and screening data (written consent) as detailed in section 4.1.1.

Interview data collected as part of the qualitative sub-study described in section 4.2.5 will be stored in password protected files within a secure Barts Trust network, only accessible to authorised personnel.

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 sponsor/Conditions 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 outcome, disease severity, engagement with diagnostic and prognostic tests, compliance with clinical management plan, adherence to therapy and outcome of therapy will be captured on eCRFs. Additional parameters relating to the cost effectiveness of the intervention will be documented. For example:

- Rate of missed appointments
- Location of consultation
- Duration of each consultation
- Job role of each health care professional providing care (specialist nurse/consultant/registrar)

All CRF data will be pseudonymised and will not be identifiable to anyone outside of the clinical care team.

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 PCTU SOPs.

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 the prevalence 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	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The

			the reasons for the urgent safety measures and the plan for future action.	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 included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor

Appendix 2: Countries listed by WHO as having >2% HBV prevalence

AFRICA

North Africa	East Africa	Southern Africa	West Africa	Central Africa
Algeria	Burundi	Botswana	Benin	Angola
Egypt	Comoros	Lesotho	Burkina Faso	Cameroon
Libyan Arab Jamahiriya	Djibouti	Namibia	Cape Verde	Central African Republic
Morocco	Eritrea	South Africa	Cote d'Ivoire	Chad
Tunisia	Ethiopia	Swaziland	Gambia	Congo
	Kenya	Zimbabwe	Ghana	D.R of the Congo
	Madagascar		Guinea	Equatorial Guinea
	Malawi		Guinea-Bissau	Gabon
	Mauritius		Liberia	Sudan
	Mozambique		Mali	Zambia
	Reunion		Mauritania	
	Rwanda		Niger	
	Seychelles		Nigeria	
	Somalia		Sao Tome and Principe	
	Uganda		Senegal	
	United R. of Tanzania		Sierra Leone	
			Togo	

Europe

Eastern Europe and Newly Independent States of the former Soviet Union	Western Europe
Albania	Greece
Armenia	Italy
Azerbaijan	Malta
Belarus	Portugal
Bosnia and Herzegovina	Spain
Bulgaria	
Croatia	
Czech Republic	
Estonia	
Georgia	
Kazakhstan	
Kyrgyzstan	
Latvia	
Lithuania	
Poland	
Republic of Moldova	
Romania	
Russian Federation	
Slovakia	
Tajikistan	
TFYR Macedonia	
Turkmenistan	
Ukraine	
Uzbekistan	
Yugoslavia	

The Americas

Mexico and Central America	Temperate South America	Tropical South America
Belize	Argentina	Bolivia
Guatemala		Brazil
Honduras		Ecuador
Mexico		Guyana
Panama		Suriname
		Venezuela

Others

The Caribbean	**Australia and the South Pacific Islands**
Antigua and Barbuda	American Samoa
Dominica	C.N. Mariana Islands
Dominican Republic	Cook Islands
Grenada	Fiji
Haiti	French Polynesia
Jamaica	Guam
Puerto Rico	Kiribati
Saint Kitts and Nevis	Marshall Islands
Saint Lucia	Micronesia
St Vincent & Grenadines	Nauru
Trinidad and Tobago	New Caledonia
Turcs and Caicos Islands	Niue
	Palau
	Papua New Guinea
	Samoa
	Solomon Islands
	Tonga
	Tuvalu
	Vanuatu
	Wallis and Futuna Islands

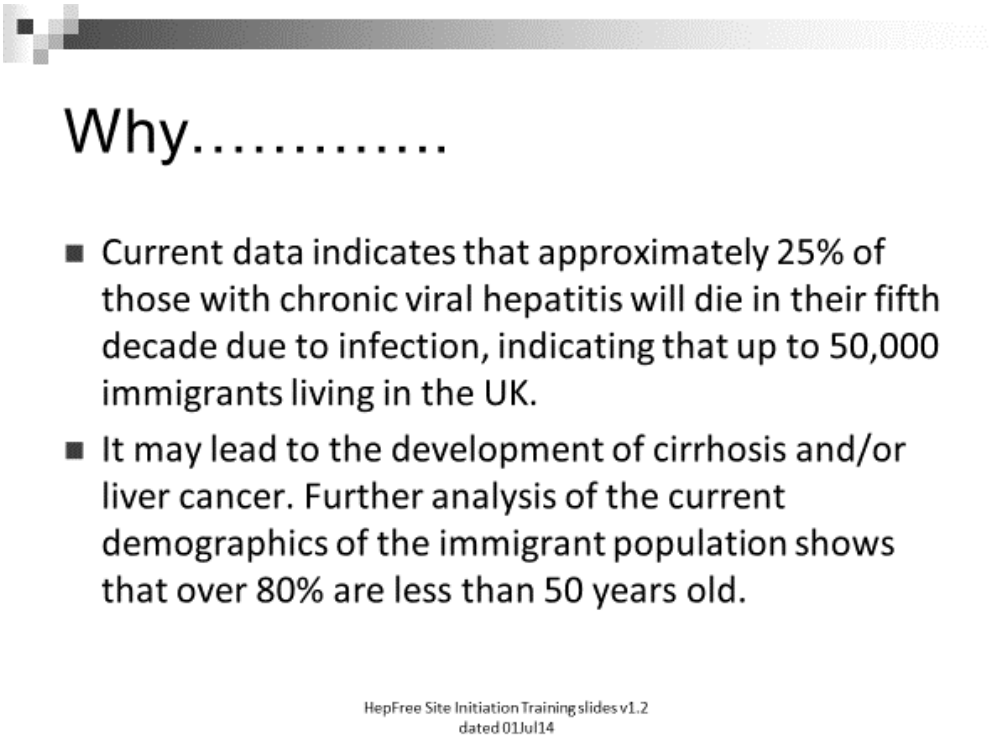
Asia

East Asia	**South East Asia**
China	Brunei
Japan	Cambodia
Dem. People's Rep. of Korea	Indonesia
Republic of Korea	Lao People's Dem. Rep.
Mongolia	Malaysia
	Myanmar (Burma)
Indian Subcontinent and South Asia	Philippines
Afghanistan	Singapore
Bangladesh	Thailand
Bhutan	Vietnam
India	
Maldives	
Nepal	
Pakistan	

Middle East

Bahrain	Oman
Iran (Islamic Republic of)	Qatar
Iraq	Saudi Arabia
Israel	Syrian Arab Republic
Jordan	Turkey
Kuwait	United Arab Emirates
Lebanon	Yemen

Appendix 3: Site Initiation Visit Slides and Handouts



The Aim

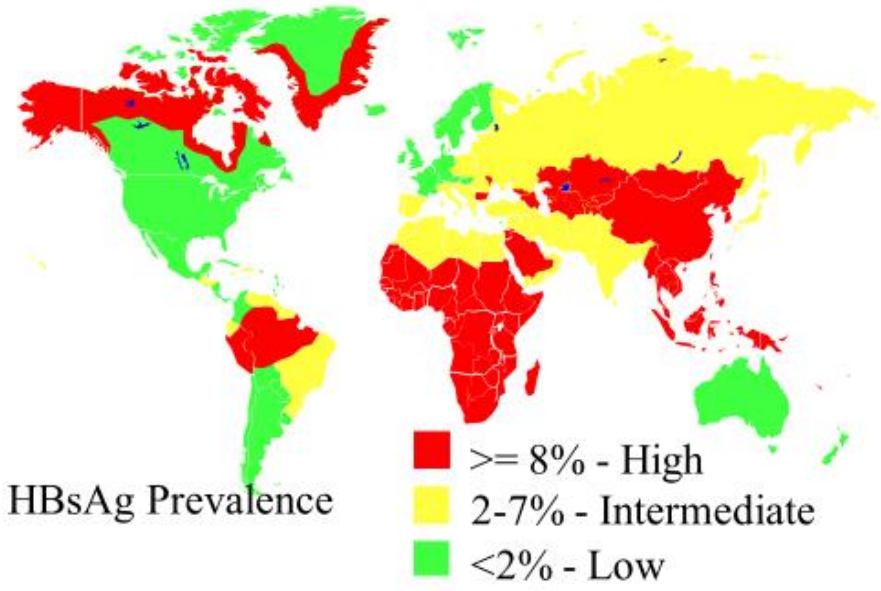
- We are hoping to recruit 55 GP practices within areas with an established immigrant (first/second generation (WHO classification of HBV prevalence >2%) population, namely in East and South London as well as Bradford.

Who is Eligible?

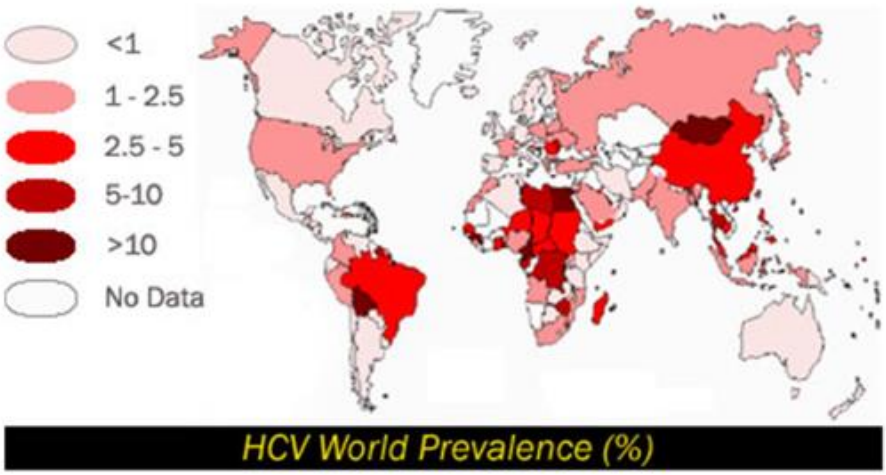
- **Inclusion Criteria:-**
- - Female and male patients who have been identified as first generations immigrants born in a country of high risk or second generation immigrants. (as outlined by WHO classification of HBV prevalence >2%)
- - >18 years of age

- **Exclusion Criteria**
- -<18 years old
- - Lacking capacity

HBV Prevalence



HCV Prevalence



HepFree Objectives

Primary Objectives

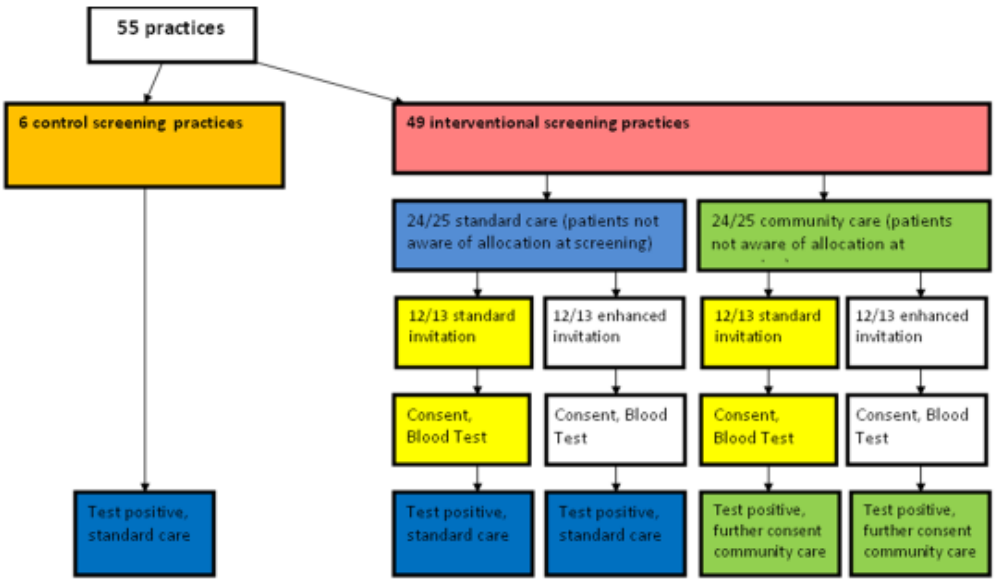
- To determine whether interventional screening is more cost-effective than control screening in the detection of viral hepatitis in ethnic minority patients in primary care.
- To determine whether the provision of an enhanced patient information invitation letters increases attendance for testing when compared to standard information invitation letter.
- 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 v1.2
dated 01Jul14

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 v1.2
dated 01Jul14

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 v1.2
dated 01Jul14

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 (please see template screenshots and annotated instructions).
- Assistance as needed 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 4 Trial Invitation Letters – Standard and Enhanced Versions

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

[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 Hep Free/ QMUL rep

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 5 – 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 6 – HepFREE Screening Trial Consent Form

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** (version 5.0) 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 London or 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 Care Information 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 (if different from investigator)	Date	Signature
_____	_____	_____
Investigator	Signature	Date

Appendix 7 – Supplementary Patient Information Sheet for Community Care

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.

2.0 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.

4.0 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.

5.0 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.

6.0 What happens when the research study stops?

Nothing, you will continue to receive your clinical standard of care for your viral hepatitis.

7.0 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

8.0 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.

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 8 – Supplementary Informed Consent Form

Chronic Viral Hepatitis in First and Second Generation Immigrants from 'At Risk' countries: The HepFREE Study

Supplementary Informed Consent Form for Viral Hepatitis Positive Patients

Consent Form Version 3.0 dated 12 March 15

Name of Centre (GP practice): Participant ID for this study:

_____ _____

Please INITIAL box to indicate agreement **Initial below**

I confirm that I have read and understood the 'Supplementary Patient Information Sheet for Viral Hepatitis Positive Patients' information sheet dated 12 March 2015 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	
I agree to remain on the HepFREE Study which will involve randomly (by chance) being assigned to receive treatment at a local hospital or at a local community care practice. I understand that the clinical care I receive will be the same, regardless of where I get treated.	

_____ _____ _____

Name of Participant Date Signature

_____ _____ _____

Name of Person taking consent Date Signature

(if different from investigator)

_____ _____ _____

Investigator Date

Signature

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.

The HepFREE Trial

Standard operating procedure document for the treatment of participants allocated to the community treatment arm of the trial in East London

Document outline

This will act as a standard operating procedure document designed as an aid for the assessment, treatment and management of patients diagnosed with chronic hepatitis B or hepatitis C virus (HBV and HCV) infection through the HepFREE trial, and assigned to the community based treatment arm of the study. The flow charts will provide time lines to indicate key follow up appointments required in the treatment of HBV and HCV and appointments required to meet the primary objectives set by the study. The document is designed to use in conjunction with Barts Health NHS Trust clinical guidelines for the management of chronic viral hepatitis.

Study objectives

- One of the primary objectives of the HepFREE study is to determine whether community based therapy is superior to conventional delivery of treatment as measured by engagement with management and treatment.
- Engagement with the study is defined completion of at least three visits for diagnosis, investigation and management in a 12 month period:
    - For patients who test HBsAg positive, or HCV Antibody, RNA positive this is attending (i) diagnostic visit (i) prognostic investigation: ultrasound and/or Fibroscan® (iii) management visit
    - NB Patients who test HCV antibody positive or equivocal but HCV RNA negative engagement is defined as attending the GP practice or the local hospital on two separate occasions.
- Compliance with the clinical management plan is defined as attending at least one visit after the management plan is agreed by participant and clinicians.
- Adherence to therapy in the study is defined as 80% completion of prescribed therapy.
- The outcome of therapy will also be monitored. A successful outcome of therapy will be defined as sustained viral response 12 weeks after treatment completion for HCV infected patients. The definition of successful outcome of therapy for HBV treatment is a reduction in viral load to <80% of starting value within 12 weeks.

Terms used

ALT	Alanine transaminase
AST	Aspartate aminotransferase
DNA	Did Not Attend (appointment)
FBC	Full blood count
FU	Follow up
G1	Genotype 1 hepatitis C virus infection
G3	Genotype 3 hepatitis C virus infection
GCSF	Granulocyte-colony stimulating factor
GP	General Practitioner
HBV	Hepatitis B infection
HCV	Hepatitis C Infection
LFTs	Liver function tests
MDT	Multidisciplinary team
ODN	Operational Delivery Network
PC	Primary care
PCR	Polymerase chain reaction
SC	Secondary care
SOC	Standard of care
SVR	Sustained virological response
TBA	To be arranged
TFTs	Thyroid function tests
Tx	Treatment
U&E	Urea and electrolytes
VHS	Viral Hepatitis Service (clinical fellow and nurse specialists)
VL	Viral load

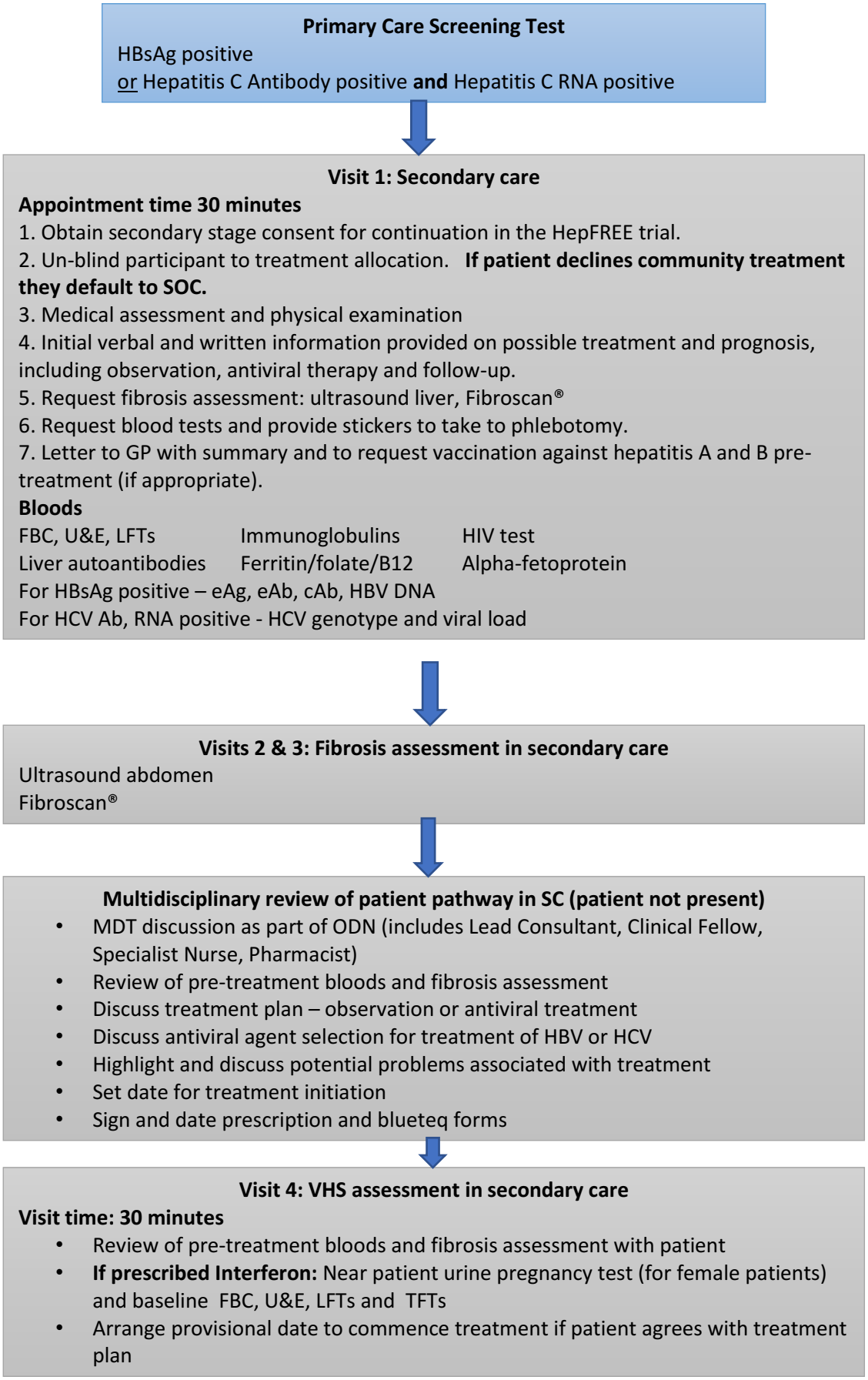
Inclusion and exclusion criteria

Care of patients allocated to community based treatment will be coordinated by the viral hepatitis service clinical fellow and clinic nurse specialists (VHS), supervised in the community by a named GP and supervised remotely by a named hepatologist. Exclusion criteria exist to ensure patient safety.

Community based treatment is contraindicated in the following groups (for whom it may be unsuitable also to treat within secondary care)

- Pregnancy, considering pregnancy or breast feeding
- Significant psychiatric history, severe depressive illness or para-suicide
- Co-existent autoimmune hepatitis or other autoimmune conditions
- Pre-existing thyroid disease, not controlled on medications
- Severe, unstable or poorly controlled cardiac disease
- Poorly controlled or unstable epilepsy.
- Retinopathy
- Evidence of decompensated liver disease or a documented previous episode of decompensation
- Alcohol intake exceeding recommended guidelines
- Evidence of impending cirrhosis:
    - Platelet count <150 $x10^9$/l
    - Albumin <35g/L
    - Evidence of portal hypertension on imaging or endoscopy.
- A low neutrophil count
- Chronic renal failure or a creatinine clearance of less than 50mls/min
- Haemoglobinopathies
- Co-infection with hepatitis B or HIV

Figure 1: Algorithm for the Assessment and Treatment of Patients with Chronic HBV or HCV infection



Visit 5: Initiation of treatment (visit 1 in primary care)

Visit time: 45 minutes

- Prior to visit: VHS to prescribe antiviral therapy, processing and checking for drug-drug interactions and dispensing of the medications from the hospital pharmacy.
- VHS to collect prescription for weeks 1-4 of treatment from the hospital pharmacy and take to patient in PC.
- Agree time, date and location of Weeks 2 & 4 visits with patient and GP practice.
- **If prescribed interferon:** Teaching session on administration of interferon, safe disposal of sharps and storage of interferon therapy
- Administer first interferon injection during consultation

Subsequent visits (follow up): Weeks 2 & 4

Visit time: 45 minutes

- Review of patient and treatment side effects.
- Check adherence to prescribed medication
- Named GP for review of acute symptoms not associated to treatment
- Prescription for symptomatic medications if required.
- At week 4 VHS to collect prescription for weeks 5-8 of treatment from the hospital pharmacy and take to patient in PC.
- Agree time, date and location of Weeks 8, 12, 24 visits with patient and GP practice.

Venepuncture by VHS for

Week 2 & 4: FBC, U&E, LFTs

Addition al Week 4 Bloods

- for Interferon Treatment: TFTs
- for HBV Infection : HBV DNA level
- for HCV Infection: HCV RNA level

Blood samples to be returned in person for processing at Royal London Hospital.

MDT review of week 4 blood results in SC

HBV infected patients on anti-virals

<1 Log drop in HBV viral load – STOP TREATMENT AND RE-REFER TO SC

HCV infected patients on treatment

<1 Log drop in HCV viral load – STOP TREATMENT AND RE-REFER TO SC

If patient has DNA'd x 2 attendances – STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC

1. HBV Infection for observation

2. HBV Infection on treatment

3. HCV Infection on treatment

1. HBV Infection for Observation

Treatment follow up for participants under observation for HBV infection
Follow up visits: 30 minutes
Weeks: 12 & 24

- Patient review
- Venepuncture:
  Week 12: FBC, U&E, LFTs
  Week 24: FBC, U&E, LFTs, AFP, HBV DNA, and request US Liver

If blood results within normal limits and US Liver shows no cirrhosis and no hepatoma, patient can be followed-up on a six-monthly basis in Community Clinic until study end.
If blood results or ultrasound report abnormal - STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC
If patient has DNA'd x 2 attendances – STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC

2. HBV Infection on Antivirals

Treatment follow up for participants prescribed antiviral therapy for HBV infection
Follow up visits: 30 minutes
Weeks: 12 & 24

- Patient review
- Venepuncture:
  Week 12: FBC, U&E, LFTs
  Week 24: FBC, U&E, LFTs, AFP, HBV DNA, and request US Liver
  Additional bloods for Interferon Treatment: TFTs

If blood results within normal limits and US Liver shows no cirrhosis and no hepatoma, patient can be followed-up on a six-monthly basis in Community Clinic until study end.
If blood results or ultrasound report abnormal - STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC
If patient has DNA'd x 2 attendances – STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC

3A. HCV Infection on DAA Therapy

Genotype 1 HCV infection treatment regimens

Treatment follow up for participants receiving HARVONI therapy
Weeks: 1, 2, 4 as above
Week 8
Visit time: 30 minutes

- VHS to collect and supply 4 weeks of antiviral therapy
- Review of patient and treatment side effects.
- Check adherence to prescribed medication
- Named GP for review of acute symptoms not associated to treatment
- Prescription for symptomatic medications if required.

Venepuncture by VHS for
FBC, U&E, LFTs, HCV RNA level
Blood samples to be returned in person for processing at Royal London Hospital.

Week 12: End of Treatment
Stop HARVONI
Patient review
Venepuncture: FBC, LFT, U&E, HCV PCR
Week 16: SVR4 Monitoring Visit
Patient review
Venepuncture: FBC, LFT, U&E, HCV PCR
Week 24: End of Monitoring
Patient review
Venepuncture: FBC, LFT, U&E, TFTs, HCV PCR
If HCV DNA level = 0, and baseline imaging showed NO CIRRHOSIS:
SVR12 achieved and patient can be followed-up at Week 48 for repeat HCV DNA prior to discharge (as per NHSE guidelines). Patient should be advised they have been CURED of HCV.
If HCV DNA level = 0 and baseline imaging showed CIRRHOSIS (compensated):
SVR12 achieved and patient can be followed-up at Week 48 and 6 monthly thereafter for repeat HCV DNA and Ultrasound level for HCC surveillance. Patient should be advised they have been CURED of HCV.

Genotype 3 HCV infection treatment regimen

Treatment follow up for participants receiving Interferon and Ribavirin therapy

Weeks: 1, 2, 4 as above

Week 8

- VHS to collect and supply 4 weeks of antiviral therapy
- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs
- Pregnancy test if appropriate

Week 12

- **If intention to treat for 12 weeks**: stop all therapy
- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level
- **If intention to treat 24weeks:**
- VHS nurse to supply a further 4 weeks of medication

Week 12 PCR review: IF LESS THAN 2 LOG DROP IN HCV VIRAL LOAD OR INCREASE IN VIRAL LOAD CONSIDER STOPPING ALL THERAPY AND REFER TO SC

Weeks 16 & 20

- VHS to collect and supply 4 weeks of antiviral therapy
- Patient review
- Venepuncture as per table below
- Pregnancy test if appropriate

Week 24: end of treatment

- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level
- Pregnancy test if appropriate

Week 28: SVR4 Monitoring Visit

- Patient review
- Venepuncture: FBC, LFT, U&E, HCV RNA level

Week 36: SVR12 Monitoring Visit

- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level

Week 48: SVR24 Monitoring Visit

- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level

If HCV DNA level = 0, and baseline imaging showed NO CIRRHOSIS:

SVR24 achieved and patient can be advised they have been CURED of HCV and discharged to GP care.

If HCV DNA level = 0 and baseline imaging showed CIRRHOSIS (compensated):

SVR24 achieved and patient can be followed-up 6 monthly thereafter for repeat HCV DNA and Ultrasound level for HCC surveillance. Patient should be advised they have been CURED of HCV.

Additional supportive measures

Use of erythropoietin or granulocyte-colony stimulating factors (GCSF)

- The follow up frequency will change to one encounter once every two weeks for patients requiring darbepoetin or GCSF for the management of anaemia or neutropenia.
- Abnormal blood tests prompting the use of these products are discussed with the named hepatologist prior to commencement, after dose reduction of ribavirin has occurred.
- G-CSF and darbepoetin will be taken to the appointment by VHS and administered during the consultation.

Issue of MED3 sickness certification

- A patient receiving antiviral therapy may require a period of time off work due to either
- Side effects of treatment or n acute medical problem.
- If the time off is due to an acute medical problem which is addressed and managed by the named GP, a MED3 certificate will be provided by the clinician.
- If the time off is due to side effects of antiviral treatment the case will be discussed at the SC MDT and a certificate issued if appropriate.

Non-attendance 'DNA'

- If a patient receiving antiviral therapy fails to attend follow up in the community during a week required for receiving prescribed medication, the patient should be contacted by phone and offered a SC appointment.
- If a patient receiving antiviral therapy fails to attend follow up in the community during a week required for monitoring of therapy the patient should be contacted by phone and offered another appointment the following week in the community centre.
- If they patient DNAs the second appointment slot, a SC appointment will be booked.

Secondary Care Visits

The purpose of starting the treatment pathway in secondary care is because the participant, at the point of entering the HepFREE trial is 'blind' to their allocation of either SOC or community based treatment.

At the index diagnostic assessment supplementary consent will be sought and participants un-blinded to their treatment allocation.

If consent is with-held the patient will be removed from the study and subsequent management performed as SOC.

The fibrosis assessment and initial viral hepatitis clinical nurse specialist assessment will be carried out in secondary care to ensure all participants have standard work up and characterisation of their liver disease prior to consideration of antiviral therapy.

Once these visits have been completed, cases will be discussed at the SC MDT meeting and a treatment pathway signed with intention to treat details.

At this point the participants contact with secondary care ends unless:

- They develop a complication preventing on-going treatment in the community
- They have evidence of significant fibrosis or cirrhosis on Fibroscan® (F3-F4) which will require follow up post treatment (at which point they will be offered a SC appointment in Hepatology Outpatient Clinic).

Location of community based treatment service

The community based treatment services in East London will be held at:

- Jubilee Street Practice, 367-374 Commercial Road, London E1 0LS
- Dr Abiola Practice, Lord Lister Health Centre, 121 Woodgrange Road, London E7 0EP
- St Andrews Health Centre, 2 Hannaford Walk Bow, London E3 3FF

Record Keeping

The individual treatment pathway will be kept in SC with VHS and taken in a secure bag to the clinic. An entry will be made in the medical record at the associated SC centre (Cerner Millennium Electronic Patient Record at the Royal London Hospital).

Emergency contact details

As per patients treated in SC, a phone number for the viral hepatitis nurses will be provided to all patients.

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.

The HepFREE Trial

Standard operating procedure document for the treatment of participants allocated to the community treatment arm of the trial in South London

Document outline

This will act as a standard operating procedure document designed as an aid for the assessment, treatment and management of patients diagnosed with chronic hepatitis B or hepatitis C virus (HBV and HCV) infection through the HepFREE trial, and assigned to the community based treatment arm of the study. The flow charts will provide time lines to indicate key follow up appointments required in the treatment of HBV and HCV and appointments required to meet the primary objectives set by the study. The document is designed to use in conjunction with Barts Health NHS Trust clinical guidelines for the management of chronic viral hepatitis.

Study objectives

- One of the primary objectives of the HepFREE study is to determine whether community based therapy is superior to conventional delivery of treatment as measured by engagement with management and treatment.
- Engagement with the study is defined completion of at least three visits for diagnosis, investigation and management in a 12 month period:
    - For patients who test HBsAg positive, or HCV Antibody, RNA positive this is attending (i) diagnostic visit (i) prognostic investigation: ultrasound and/or Fibroscan® (iii) management visit
    - NB Patients who test HCV antibody positive or equivocal but HCV RNA negative engagement is defined as attending the GP practice or the local hospital on two separate occasions.
- Compliance with the clinical management plan is defined as attending at least one visit after the management plan is agreed by participant and clinicians.
- Adherence to therapy in the study is defined as 80% completion of prescribed therapy.
- The outcome of therapy will also be monitored. A successful outcome of therapy will be defined as sustained viral response 12 weeks after treatment completion for HCV infected patients. The definition of successful outcome of therapy for HBV treatment is a reduction in viral load to <80% of starting value within 12 weeks.

Terms used

ALT	Alanine transaminase
AST	Aspartate aminotransferase
DNA	Did Not Attend (appointment)
FBC	Full blood count
FU	Follow up
G1	Genotype 1 hepatitis C virus infection
G3	Genotype 3 hepatitis C virus infection
GCSF	Granulocyte-colony stimulating factor
GP	General Practitioner
HBV	Hepatitis B infection
HCV	Hepatitis C Infection
LFTs	Liver function tests
MDT	Multidisciplinary team
ODN	Operational Delivery Network
PC	Primary care
PCR	Polymerase chain reaction
SC	Secondary care
SOC	Standard of care
SVR	Sustained virological response
TBA	To be arranged
TFTs	Thyroid function tests
Tx	Treatment
U&E	Urea and electrolytes
VHS	Viral Hepatitis Service (clinical fellow and nurse specialists)
VL	Viral load

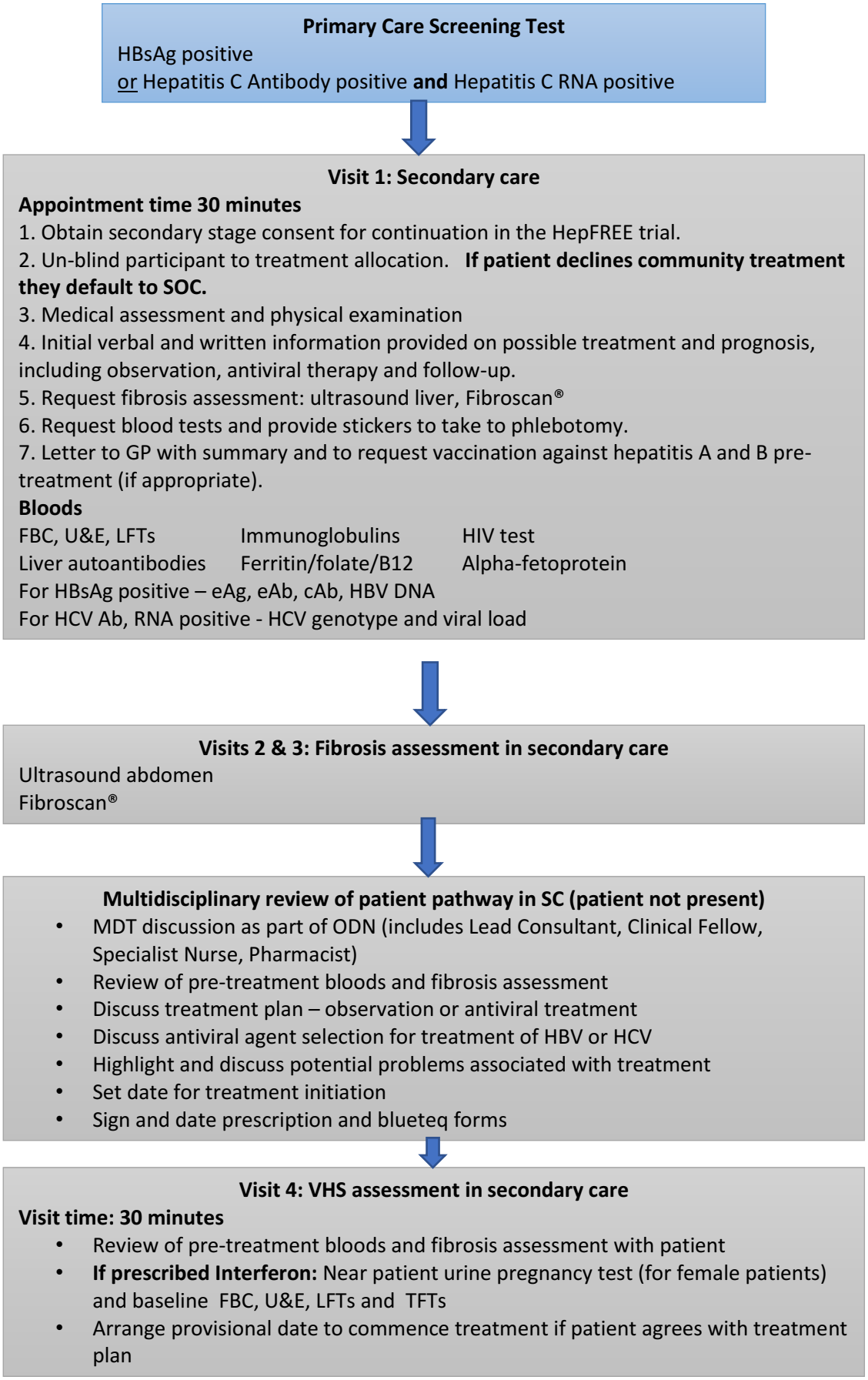
Inclusion and exclusion criteria

Care of patients allocated to community based treatment will be coordinated by the viral hepatitis service clinical fellow and clinic nurse specialists (VHS), supervised in the community by a named GP and supervised remotely by a named hepatologist. Exclusion criteria exist to ensure patient safety.

Community based treatment is contraindicated in the following groups (for whom it may be unsuitable also to treat within secondary care)

- Pregnancy, considering pregnancy or breast feeding
- Significant psychiatric history, severe depressive illness or para-suicide
- Co-existent autoimmune hepatitis or other autoimmune conditions
- Pre-existing thyroid disease, not controlled on medications
- Severe, unstable or poorly controlled cardiac disease
- Poorly controlled or unstable epilepsy.
- Retinopathy
- Evidence of decompensated liver disease or a documented previous episode of decompensation
- Alcohol intake exceeding recommended guidelines
- Evidence of impending cirrhosis:
    - Platelet count <150 $x10^9$/l
    - Albumin <35g/L
    - Evidence of portal hypertension on imaging or endoscopy.
- A low neutrophil count
- Chronic renal failure or a creatinine clearance of less than 50mls/min
- Haemoglobinopathies
- Co-infection with hepatitis B or HIV

Figure 1: Algorithm for the Assessment and Treatment of Patients with Chronic HBV or HCV infection



Visit 5: Initiation of treatment (visit 1 in primary care)

Visit time: 45 minutes

- Prior to visit: VHS to prescribe antiviral therapy, processing and checking for drug-drug interactions and dispensing of the medications from the hospital pharmacy.
- VHS to collect prescription for weeks 1-4 of treatment from the hospital pharmacy and take to patient in PC.
- Agree time, date and location of Weeks 2 & 4 visits with patient and GP practice.
- **If prescribed interferon:** Teaching session on administration of interferon, safe disposal of sharps and storage of interferon therapy
- Administer first interferon injection during consultation

Subsequent visits (follow up): Weeks 2 & 4

Visit time: 45 minutes

- Review of patient and treatment side effects.
- Check adherence to prescribed medication
- Named GP for review of acute symptoms not associated to treatment
- Prescription for symptomatic medications if required.
- At week 4 VHS to collect prescription for weeks 5-8 of treatment from the hospital pharmacy and take to patient in PC.
- Agree time, date and location of Weeks 8, 12, 24 visits with patient and GP practice.

Venepuncture by VHS for

Week 2 & 4: FBC, U&E, LFTs

Addition al Week 4 Bloods

- for Interferon Treatment: TFTs
- for HBV Infection : HBV DNA level
- for HCV Infection: HCV RNA level

Blood samples to be returned in person for processing at King's College London

MDT review of week 4 blood results in SC

HBV infected patients on anti-virals

<1 Log drop in HBV viral load – STOP TREATMENT AND RE-REFER TO SC

HCV infected patients on treatment

<1 Log drop in HCV viral load – STOP TREATMENT AND RE-REFER TO SC

If patient has DNA'd x 2 attendances – STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC

1. HBV Infection for observation

2. HBV Infection on treatment

3. HCV Infection on treatment

1. HBV Infection for Observation

Treatment follow up for participants under observation for HBV infection
Follow up visits: 30 minutes
Weeks: 12 & 24

- Patient review
- Venepuncture:
  Week 12: FBC, U&E, LFTs
  Week 24: FBC, U&E, LFTs, AFP, HBV DNA, and request US Liver

If blood results within normal limits and US Liver shows no cirrhosis and no hepatoma, patient can be followed-up on a six-monthly basis in Community Clinic until study end.
If blood results or ultrasound report abnormal - STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC
If patient has DNA'd x 2 attendances – STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC

2. HBV Infection on Antivirals

Treatment follow up for participants prescribed antiviral therapy for HBV infection
Follow up visits: 30 minutes
Weeks: 12 & 24

- Patient review
- Venepuncture:
  Week 12: FBC, U&E, LFTs
  Week 24: FBC, U&E, LFTs, AFP, HBV DNA, and request US Liver
  Additional bloods for Interferon Treatment: TFTs

If blood results within normal limits and US Liver shows no cirrhosis and no hepatoma, patient can be followed-up on a six-monthly basis in Community Clinic until study end.
If blood results or ultrasound report abnormal - STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC
If patient has DNA'd x 2 attendances – STOP COMMUNITY FOLLOW-UP and RE-REFER TO SC

3A. HCV Infection on DAA Therapy

Genotype 1 HCV infection treatment regimens

Treatment follow up for participants receiving HARVONI therapy
Weeks: 1, 2, 4 as above
Week 8
Visit time: 30 minutes

- VHS to collect and supply 4 weeks of antiviral therapy
- Review of patient and treatment side effects.
- Check adherence to prescribed medication
- Named GP for review of acute symptoms not associated to treatment
- Prescription for symptomatic medications if required.

Venepuncture by VHS for
FBC, U&E, LFTs, HCV RNA level
Blood samples to be returned in person for processing at Royal London Hospital.

Week 12: End of Treatment
Stop HARVONI
Patient review
Venepuncture: FBC, LFT, U&E, HCV PCR
Week 16: SVR4 Monitoring Visit
Patient review
Venepuncture: FBC, LFT, U&E, HCV PCR
Week 24: End of Monitoring
Patient review
Venepuncture: FBC, LFT, U&E, TFTs, HCV PCR
If HCV DNA level = 0, and baseline imaging showed NO CIRRHOSIS:
SVR12 achieved and patient can be followed-up at Week 48 for repeat HCV DNA prior to discharge (as per NHSE guidelines). Patient should be advised they have been CURED of HCV.
If HCV DNA level = 0 and baseline imaging showed CIRRHOSIS (compensated):
SVR12 achieved and patient can be followed-up at Week 48 and 6 monthly thereafter for repeat HCV DNA and Ultrasound level for HCC surveillance. Patient should be advised they have been CURED of HCV.

Genotype 3 HCV infection treatment regimen

Treatment follow up for participants receiving Interferon and Ribavirin therapy

Weeks: 1, 2, 4 as above

Week 8

- VHS to collect and supply 4 weeks of antiviral therapy
- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs
- Pregnancy test if appropriate

Week 12

- **If intention to treat for 12 weeks**: stop all therapy
- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level
- **If intention to treat 24weeks:**
- VHS nurse to supply a further 4 weeks of medication

Week 12 PCR review: IF LESS THAN 2 LOG DROP IN HCV VIRAL LOAD OR INCREASE IN VIRAL LOAD CONSIDER STOPPING ALL THERAPY AND REFER TO SC

Weeks 16 & 20

- VHS to collect and supply 4 weeks of antiviral therapy
- Patient review
- Venepuncture as per table below
- Pregnancy test if appropriate

Week 24: end of treatment

- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level
- Pregnancy test if appropriate

Week 28: SVR4 Monitoring Visit

- Patient review
- Venepuncture: FBC, LFT, U&E, HCV RNA level

Week 36: SVR12 Monitoring Visit

- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level

Week 48: SVR24 Monitoring Visit

- Patient review
- Venepuncture: FBC, LFT, U&E, TFTs, HCV RNA level

If HCV DNA level = 0, and baseline imaging showed NO CIRRHOSIS:
SVR24 achieved and patient can be advised they have been CURED of HCV and discharged to GP care.

If HCV DNA level = 0 and baseline imaging showed CIRRHOSIS (compensated):
SVR24 achieved and patient can be followed-up 6 monthly thereafter for repeat HCV DNA and Ultrasound level for HCC surveillance. Patient should be advised they have been CURED of HCV.

Additional supportive measures

Use of erythropoietin or granulocyte-colony stimulating factors (GCSF)

- The follow up frequency will change to one encounter once every two weeks for patients requiring darbepoetin or GCSF for the management of anaemia or neutropenia.
- Abnormal blood tests prompting the use of these products are discussed with the named hepatologist prior to commencement, after dose reduction of ribavirin has occurred.
- G-CSF and darbepoetin will be taken to the appointment by VHS and administered during the consultation.

Issue of MED3 sickness certification

- A patient receiving antiviral therapy may require a period of time off work due to either
- Side effects of treatment or n acute medical problem.
- If the time off is due to an acute medical problem which is addressed and managed by the named GP, a MED3 certificate will be provided by the clinician.
- If the time off is due to side effects of antiviral treatment the case will be discussed at the SC MDT and a certificate issued if appropriate.

Non-attendance 'DNA'

- If a patient receiving antiviral therapy fails to attend follow up in the community during a week required for receiving prescribed medication, the patient should be contacted by phone and offered a SC appointment.
- If a patient receiving antiviral therapy fails to attend follow up in the community during a week required for monitoring of therapy the patient should be contacted by phone and offered another appointment the following week in the community centre.
- If they patient DNAs the second appointment slot, a SC appointment will be booked.

Secondary Care Visits

The purpose of starting the treatment pathway in secondary care is because the participant, at the point of entering the HepFREE trial is 'blind' to their allocation of either SOC or community based treatment.

At the index diagnostic assessment supplementary consent will be sought and participants un-blinded to their treatment allocation.

If consent is with-held the patient will be removed from the study and subsequent management performed as SOC.

The fibrosis assessment and initial viral hepatitis clinical nurse specialist assessment will be carried out in secondary care to ensure all participants have standard work up and characterisation of their liver disease prior to consideration of antiviral therapy.

Once these visits have been completed, cases will be discussed at the SC MDT meeting and a treatment pathway signed with intention to treat details.

At this point the participants contact with secondary care ends unless:

- They develop a complication preventing on-going treatment in the community
- They have evidence of significant fibrosis or cirrhosis on Fibroscan® (F3-F4) which will require follow up post treatment (at which point they will be offered a SC appointment in Hepatology Outpatient Clinic).

Location of community based treatment service

The community based treatment services in East London will be held at:

- Albion Street Group Practice, 87 Albion St, London SE16 7JX
- Manor Place Surgery, 1 Manor Place, London, SE17 3BD
- Sir John Kirk Close Surgery, 3 Sir John Kirk Close, London, SE5 0BB
- Crown Dale Medical Centre, 61 Crown Dale, London, SE19 3NY

Record Keeping

The individual treatment pathway will be kept in SC with VHS and taken in a secure bag to the clinic. An entry will be made in the medical record at the associated SC centre (Sunrise Electronic Patient Record at the King's College Hospital).

Emergency contact details

As per patients treated in SC, a phone number for the viral hepatitis nurses will be provided to all patients.

Appendix 11: Pre-Screening Survey Questionnaire

VIRAL HEPATITIS B & C Survey

Date of interview: ……..	**Subject ID: ……**

Thank you very much for agreeing to take part in this interview. We are going to ask you a few questions about yourself.

PARTICIPANT INFORMATION

1: Year of birth:

2: Gender

Are you: ☐ **Male**

☐ **Female**

☐ **Transgender**

3: Where were you born? …….

4: If you were born outside UK, what year did you first come to live in the UK? …….

5: If born in the UK, where did your parent (at least one parent must be from outside the UK) come from?
……

6: **What is your religious belief?**

- ☐ **Buddhist**
- ☐ **Christian**
- ☐ **Muslim**
- ☐ **Sikh**
- ☐ **Hindu**
- ☐ **Taoist**
- ☐ **No religion**
- ☐ **Other……..**

7: What is your marital Status?

- ☐ **Married**
- ☐ **Living as married**
- ☐ **Widowed**
- ☐ **Separated**
- ☐ **Divorced**
- ☐ **Never married**
- ☐ **Other……..**

8: What is your ethnic group?
Asian /Asian British

- ☐ **Chinese**
- ☐ **Pakistani**
- ☐ **Other Asian Background**

Black / African / Black British

- ☐ **African**
- ☐ **Somali**
- ☐ **Other African background**

Any other White European

- ☐ **Polish**
- ☐ **Lithuania**
- ☐ **Romania**
- ☐ **Bulgaria**
- ☐ **Slovakia**
- ☐ **Other European …….**

Mixed / multiple ethnic groups

- ☐ **White / Pakistani**
- ☐ **White / Black African**
- ☐ **White / Chinese**
- ☐ **White / Somali**
- ☐ **Any mixed other ……..**

9: What is the language(s) mostly spoken at home?

……

10: How well would you say you speak language?

- ☐ **Fluently**
- ☐ **Well**
- ☐ **Quite well**
- ☐ **Not well**
- ☐ **No at all**
- ☐ **Other……..**

11: How well would you say you read in English?

- ☐ **Fluently**
- ☐ **Well**
- ☐ **Quite well**
- ☐ **Not well**
- ☐ **No at all**
- ☐ **Other……..**

12: Which of these qualifications do you have?

- **Tick every box that applies if you have any other qualifications listed**
- **If your qualification is not listed, tick the box that contains its nearest equivalent**

If you have qualifications gained outside the UK, tick the 'Foreign qualifications' box and the nearest UK equivalents (if known)

- ☐ **1-4 O levels /CSEs/GSEs (any grades), Entry level, Foundation diploma**
- ☐ **NVQ Level 1, Foundation GNVQ, Basic Skills**
- ☐ **5+ O level (passes) / CSEs (grade1) / GCSEs (grades A*-C), School Certificate, 1A levels/ 2-3 AS levels / VCEs, Higher Diploma**
- ☐ **NVQ Level 2, Intermediate GNVQ, City and Guilds Advanced Craft, BTEC First / General National, RSA Diploma**
- ☐ **Apprenticeship**
- ☐ **2+ A levels/VCEs, 4+ AS levels, Higher School certificate, Progression / Advanced Diploma**
- ☐ **NVQ Level 3, Advanced GNVQ, City and Guilds Advanced Craft, ONC, OND, BTEC national, RSA Advanced Diploma**
- ☐ **Degree (for example BA, BSc), Higher Education (For example, MA, PhD, PGCE)**
- ☐ **NVQ Level 4-5, HNC, HND, RSA Higher Diploma, BTEC Higher Level**
- ☐ **Professional qualifications (For example teaching, nursing, accountancy)**
- ☐ **Other vocational / work-related qualifications**
- ☐ **Foreign qualifications**
- ☐ **No qualifications**
- ☐ **Other**

13: Are you currently

- ☐ **Employed**
- ☐ **Self-employed**
- ☐ **Housewife**
- ☐ **Unemployed**
- ☐ **Student**
- ☐ **Other**

14: What type housing do you live in?

- ☐ **A council flat / house**
- ☐ **A privately rented flat / house**
- ☐ **Owned house / flat**
- ☐ **Other…….**

15: Would you mind estimating the approximate total income of your household members during the last year? Income includes money from things like state benefits (income support, housing benefit, child benefit, disability living allowances), and wages.

- ☐ **Less than £10,000**
- ☐ **Between £10,000 and £20,000**
- ☐ **Between £20,000 and £30,000**
- ☐ **Between £30,000 and £40,000**
- ☐ **Between 40,000 and £50, 000**
- ☐ **Over £50,000**
- ☐ **Other……..**

16: How is your health?

- ☐ **Very good**
- ☐ **Good**
- ☐ **Fair**
- ☐ **Bad**
- ☐ **Very bad**
- ☐ **Other…….**

17: Have you visited a Doctor / GP over the last six months?

☐ **Yes**

☐ **No**

☐ **Other** ……..

18: How many children (below 16 years old) do you have in the household?

……..

19: Have you ever been tested for viral hepatitis B or C?

☐ **Yes** **Which one?.....** *[Go to question 20]*

☐ **No** *[Go to question 24]*

☐ **Do not know** *[Go to question 24]*

☐ **Other……** *[Go to question 24]*

20: If yes:
When were you tested (specify for hepatitis B or C)?

☐ **Year ……**

☐ **Do not know**

i. Where were you tested (specify for hepatitis B or C)?

☐ **UK**

☐ **Country of origin**

☐ **Other country**

☐ **Other……..**

ii. Why were you tested?

☐ **As part of a routine health check, ordered by my doctor (GP)**

☐

Community screening programme (specify)……

☐ **Ordered by hospital (because of my other illness)**

☐ **As part of occupational health / employment**

☐ **As part of a requirement for course / training**

☐ **Family member tested positive - for: hepatitis B and / or hepatitis C …..(specify)……**

☐ **Family member having liver disease**

☐ **Facilitated by self, to check if having viral hepatitis**

☐ **Do not know**

☐ **Other…….**

21: What was the outcome of the test?

☐ **Negative**

☐ **Positive**

☐ **Do not know**

☐ **Other ……**

22: If not tested, would you be willing get tested for viral hepatitis?

☐ **Yes**

☐ **No**

☐ **Other …….**

23: Has any other person in the family been tested for viral hepatitis?

☐ **Yes**

☐ **No**

☐ **Do not know**

☐ **Other…….**

24: Has a doctor, a nurse, or a healthcare provider ever recommended a test for viral hepatitis B and C?

☐ **Yes**

☐ **No** ***[go to question 27]***

☐ **Other ……..*****[go to question 27]***

25: Have you ever had vaccination (3 shots) to prevent you from getting viral hepatitis B?

☐ **No**

☐ **Yes**

☐ **Do not know**

☐ **Other …….**

26: If yes,

When were you vaccinated?

☐ **Year……**

☐ **Do not know**

Where were you vaccinated?

☐ **UK**

☐ **Country of origin**

☐ **Other country**

Why were you vaccinated?

☐ **As part of a routine health check**

☐ **Afraid of being infected with viral hepatitis B**

☐ **As part of antenatal care**

☐ **As part of occupational health for employment**

☐ **As part of a requirement for a course / training**

☐ **To prevent viral hepatitis B**

☐ **Do not know**

☐ **Other**

27: Has your doctor, a nurse, or any other healthcare provider ever recommended having vaccination for hepatitis B?

- ☐ **Yes**
- ☐ **No**
- ☐ **Other……**

28: Would be willing to get vaccinated against hepatitis B?

- ☐ **Yes**
- ☐ **No**
- ☐ **Other……**

29: Do you have a family member who has viral hepatitis B or C?

- ☐ **Yes, hepatitis B**
- ☐ **Yes, hepatitis C**
- ☐ **No**
- ☐ **Do not know**
- ☐ **Other……**

30: Do you think viral hepatitis B & C infections can cause liver cancer (/ liver disease)?

- ☐ **Yes**
- ☐ **No**
- ☐ **Do not know**
- ☐ **Other……..**

VIRAL HEPATITIS CHECKLIST

This is part of the interview is about how people understand and perceive viral hepatitis B and C infections. It is totally anonymous and confidential. We will keep no reference to your name and your answers will be combined with others before they are analysed. We are very much interested in your personal views, thoughts, and understanding. This means there is no wrong or right answers to the questions we are going to ask you.

1. ***Please could you tick any of the following boxes, what you think are the symptoms of viral hepatitis (B & C)***

☐ **Jaundice**	☐ **Headaches**
☐ **Yellow eyes**	☐ **Other……**
☐ **Greenish-yellow eyes**	
☐ **Not tolerating food with too much butter / fat**	
☐ **Yellow urine**	
☐ **Eye bag**	
☐ **Green urine**	
☐ **Abdominal pain**	
☐ **Swollen belly**	
☐ **Fatigue (looking tired)**	
☐ **Nausea (vomiting)**	
☐ **Tough liver**	
☐ **Swollen liver**	
☐ **Loss of appetite**	
☐ **Blurred vision**	

2. ***Please could you tick any of the following boxes, what you think are the causes of viral hepatitis (B & C)***

- ☐ **Damaged / weak liver**
- ☐ **Weak body**
- ☐ **Food not cooked properly**
- ☐ **Unclean / contaminated food**
- ☐ **Fried food**
- ☐ **Fatty food**
- ☐ **New foods**
- ☐ **Spicy food**
- ☐ **Seafood**
- ☐ **Dirty / contaminated vegetables / salads**
- ☐ **Butter (sheep fat)**
- ☐ **Milk**
- ☐ **Hard work / labour**
- ☐ **Alcohol**
- ☐ **Smoking cigarettes / tobacco**
- ☐ **Poor sanitation**
- ☐ **Toilets**
- ☐ **Environment**
- ☐ **Heat / sun**
- ☐ **Dirty / contaminated khat**
- ☐ **Heredity / Genes**
- ☐ **Hormones**
- ☐ **Bacteria**
- ☐ **Fate**
- ☐ **Stress**

- ☐ **Negative emotions**
- ☐ **Poor hygiene**
- ☐ **Raw food**
- ☐ **Poverty**
- ☐ **Physical deprivation**
- ☐ **Migration**
- ☐ **Lack of rest**
- ☐ **Drinking less water**
- ☐ **Malaria**
- ☐ **Other…**……

……

……

……

3. ***Please could you tick any of the following boxes, what you think about how viral hepatitis (B & C) is spread / transmitted?***

- ☐ **Sexual transmission**
- ☐ **Oral sex**
- ☐ **Tasting food while cooking**
- ☐ **Sleeping together**
- ☐ **During birth**
- ☐ **Hereditary (genes)**
- ☐ **Kissing**
- ☐ **Holding / Shaking hands**
- ☐ **Hugging**
- ☐ **Contact with open wound or open / cut skin**
- ☐ **Tattooing**
- ☐ **Body piercing**
- ☐ **Traditional healing practices**
- ☐ **Smoking**
- ☐ **Alcohol**
- ☐ **Sharing food & drinks with an infected person**
- ☐ **Sharing eating / drinking utensils**
- ☐ **Dental surgical equipment**
- ☐ **Poor hygiene practices**
- ☐ **Sharing earrings**
- ☐ **Coughing and sneezing**
- ☐ **Eating food prepared / cooked by an infected person**
- ☐ **Raw food**
- ☐ **Dirty food**
- ☐ **Contaminated food**
- ☐ **Eating pre-chewed food**
- ☐ **Mosquitoes**
- ☐ **Dirty water**
- ☐ **Not washing hands**
- ☐ **Sharing water**
- ☐ **Lancet therapy**
- ☐ **Blood and body fluids (including sweat & saliva)**
- ☐ **Sharing razor blades**
- ☐ **Sharing tooth brush**
- ☐ **Sharing water wells**
- ☐ **Organ transplant**
- ☐ **Blood transfusion**
- ☐ **Close contact with the infected**
- ☐ **Drug injecting paraphernalia – (spoon, filter, & needles)**
- ☐ **Surgical procedures**
- ☐ **Breast feeding**
- ☐ **Sharing towels**
- ☐ **Poor hygiene practices**
- ☐ **Sharing (/contaminated) syringes and needles for medical injections**
- ☐ **Sharing nail clippers**

- ☐ **Other…….**
  ……

4. Please could you tick any of the following boxes, what you think can prevent / control the spread / transmission of viral hepatitis (B & C)

- ☐ **Vaccinations**
- ☐ **Test**
- ☐ **Regular check-ups / test / screenings**
- ☐ **Good hygiene**
- ☐ **Clean food**
- ☐ **Properly cooked food**
- ☐ **Balanced diets**
- ☐ **Not sharing food and drinks**
- ☐ **Avoid eating in restaurants**
- ☐ **Not sharing utensils**
- ☐ **Cleanliness**
- ☐ **Not sharing clothes**
- ☐ **Wear clean clothes**
- ☐ **Personal hygiene / cleanliness**
- ☐ **Avoid butter / sheep fat**
- ☐ **Avoid sesame oil with beans**
- ☐ **Clean water**
- ☐ **No sex before marriage**
- ☐ **No extramarital sex**
- ☐ **Regular exercise**
- ☐ **Not sharing razor blades**
- ☐ **Sharing tooth brush**
- ☐ **Avoid travelling in a bus**
- ☐ **Avoid public places**

- ☐ **No contact with infected individuals**
- ☐ **No kissing**
- ☐ **Cover open wounds**
- ☐ **Enough rest**
- ☐ **Stress reduction**
- ☐ **Adequate sleep**
- ☐ **Indigenous (herbal) medicines**
- ☐ **Not smoking**
- ☐ **Avoid illicit drugs**
- ☐ **Avoid alcohol**
- ☐ **Avoid blood contact**
- ☐ **Avoid bodily contact**
- ☐ **Use a condom**
- ☐ **Avoid drinking contaminated water**
- ☐ **Healthy living**
- ☐ **Not sharing soap**
- ☐ **Quarantine / isolation for the infected**
- ☐ **Staying in the hospital**

Other …….

……

5. Please could you tick any of the following boxes, what you think is the course (sequelae) of viral hepatitis (B & C)

- ☐ **Liver cancer**
- ☐ **Liver cirrhosis**
- ☐ **Death**
- ☐ **Other …….**

6. Please could you tick any of the following boxes, what you think is the consequences of viral hepatitis (B & C)

- ☐ **Liver cancer**
- ☐ **Liver cirrhosis**
- ☐ **Death**
- ☐ **Lifelong infection (incurable)**
- ☐ **Worry**
- ☐ **Stress**
- ☐ **Scared**
- ☐ **Anxiety**
- ☐ **Sadness**
- ☐ **Exhaustion**
- ☐ **Depression**
- ☐ **Loss of employment**
- ☐ **Loss of future work / income / financial security**
- ☐ **Stigma**
- ☐ **Shame**
- ☐ **Fear of getting cancer / death**
- ☐ **Not able to marry / be married**
- ☐ **Being killed by family (honour killing)**
- ☐ **Discrimination**
- ☐ **Isolation from family and community**
- ☐ **Other……**

……

……

7. ***Please could you tick any of the following boxes, what you think are the ways of treating / managing viral hepatitis (B & C)***

- ☐ **Testing / screening**
- ☐ **Enough rest**
- ☐ **Regular exercise**
- ☐ **Good nutrition (balanced diet)**
- ☐ **Treatment using alternative medicine such as Traditional Chinese Medicine, & other indigenous / traditional medicines**
- ☐ **Watermelon**
- ☐ **Clean water**
- ☐ **Blood transfusion**
- ☐ **Burning area above the liver (parietal area), hands, behind knees, & head**
- ☐ **Drinking camel milk**
- ☐ **Eating lamb / sheep meat**
- ☐ **Hospital treatment with medication / tablets**
- ☐ **Spiritual healing**
- ☐ **Sugar**
- ☐ **Reduce alcohol consumption**
- ☐ **Other…….**

Thank you for your time

Queen Mary
University of London

INFORMATION SHEET

Study title: The provider experience of the 'HepFREE' viral hepatitis screening and treatment intervention in primary care – follow-up after completion of screening period

We would like to invite you to be part of this research project. You should only agree to take part in this project if you want to; it is entirely up to you.

Please read the following information before deciding to take part; this will tell you why the research is being done and what you will be asked to do if you take part. Please ask if there is anything that is not clear or if you would like more information. If you decide to take part you will be asked to sign the attached form to say that you agree. You are still free to withdraw at any time and without giving a reason.

Purpose of the study:

The purpose of the research is to explore the experiences of primary care practices following the completion of the 'HepFREE' intervention of targeted screening and treatment for chronic viral hepatitis in high-risk immigrant communities. We are interested in gathering perspectives from GPs, practice nurses, and practice managers who were involved in the 'HepFREE' study. **You are being invited to participate in an interview as part of this research** in order to explore your views on barriers and supports to delivering the intervention, and suggestions for improving the national roll-out of the service model. We hope that the results of the study will inform us in developing recommendations and resources to support primary care services in delivering interventions to manage chronic viral hepatitis in immigrant patients.

Details of participation:

If you are willing to participate in the research, you will be invited to take part in an interview with a researcher. The timing and length of this interview will be dependent upon your availability. The interview can be held by telephone if that is more convenient. As a thank you for the time taken to be interviewed, you will be offered a shopping voucher to the value of £50.

Do I have to take part?

It is up to you to decide to join the research interview. We will describe the aims of the research interview and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form and begin to conduct the interview at a time/place of convenience to you. You are free to withdraw at any time, without giving a reason.

Previous HepFREE Research Interview - "implementing and delivering the 'HepFREE' intervention"

In July – October 2014, the HepFREE team commissioned a very similar research interview called "implementing and delivering the 'HepFREE' intervention". You may or may not have participated in that research interview at the beginning of the HepFREE study in 2014. The procedures for conducting the interviews in 2014 were fully approved by the Research Ethics Committee at Queen Mary, University of London (No. QMREC2012/02). Participation in that research interview is confidential and the current research interviewer does not know whether you have previously been interviewed or not.

We are interested in linking answers from interviews conducted in 2014, as part of the "implementing and delivering the 'HepFREE' intervention" study, to these new interviews being conducted in 2016/2017, but require your explicit consent to do so.

If you have previously been interviewed and would like to provide consent for a member of the interviewing team to have access to the interview transcripts from 2014 please state your explicit consent in the consent form. If you provide consent, a member of the team analysing the interviews will analyse answers from both of the interviews but will NOT disclose your name or the GP practice where you work. If you would NOT like for the interviewer to have access to the interview conducted in July - October 2014 this does not compromise your participation in this study. You can still take part in this research interview even if you have not previously been interviewed in 2014. If you did not take part in the 2014 interviews or wish not to disclose your participation in the 2014 interviews please leave the relevant section in the consent form blank.

Will my taking part be kept confidential?

Your participation in this study will be kept confidential. All information which is collected about you during the course of the research will be kept strictly confidential. The interview will be audio-recorded, but all names and identifying information will be changed upon transcription of recordings. The study will abide by the Data Protection Act 1998, and the rights you have under this Act.

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.

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 contact:

Dr. Stuart Flanagan - 0207882 3854/ stuart.flanagan@nhs.net
Hepatology Unit,
Blizard Institute
Queen Mary University of London
4 Newark Street,
London E1 2AT

If you have any questions or concerns about the manner in which the study was conducted please, in the first instance, contact the researcher above responsible for the study. If this is unsuccessful, or not appropriate, please contact the Principal Investigator Prof. Graham Foster, Blizard Institute, Queen Mary University of London, E1 2AT g.r.foster@qmul.ac.uk

Appendix 13 – HepFREE Provider Experience Participant Consent Form version 1.0

Title of Study: ***The provider experience of the 'HepFREE' viral hepatitis screening and treatment intervention in primary care – follow-up after completion of screening period***

Consent form V1.0_dated_11Aug2016

Please complete this form after you have read the Information Sheet and/or have received an explanation about the research.

Thank you for considering taking part in this research.

Please initial box to indicate agreement

INITIAL BELOW

*I confirm that I have read and understand the information sheet dated **11Aug2016** (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.*	
I understand that if I decide at any other time during the research that I no longer wish to participate in this project, I can notify the researchers involved and be withdrawn from it immediately.	
I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.	
I wish to voluntarily disclose that I took part in the research interviews called "implementing and delivering the 'HepFREE' intervention" in 2014. I wish to give consent to the current interviewers to have access to the interview transcript from 2014 providing that they do not disclose my name or the GP Practice where I work. Transcripts from interviews held in 2014 will be held in strict confidence and in accordance with the provisions of the Data Protection Act 1998. If you did not take part in the 2014 interviews or wish not to disclose this information please do not initial this statement. You can still take part in the research interview even if you do not initial this statement.	
I understand that the interview transcripts have to be archived for 20 years and agree to this.	
I agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this research interview	

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Investigator	Date	Signature

Appendix 14 HepFREE Provider Experience Semi-Structured Interview Questions

QUESTIONS

1. Motivations & Challenges

Could you tell me how the practice's participation in the HepFREE trial has gone?
Do you think there were any benefits of the trial? (either for the practice, staff or patients)
- What were they?

Were there aspects of the trial that staff found problematic?
Were there aspects of the trial that patients found problematic?

2. Study Set-Up at Practice

Did someone take the lead for looking after HepFREE at the practice?

- We know this study required inputting of data codes on patient records - how did you and other staff member find the process of collecting data?
- Any comments on how this process compared to collection of other routine data in the practice?
- Was it straightforward or problematic?
- Why was that?
- Can you tell me more about your training experience? How do you think the training experience could be improved?

3. Patient Recruitment

What was the trial recruitment process at your practice?

Did it include

- Invitation texts?
- invitation phone calls?
- Prompted by Doctor or Nurse testing?

What was the patient response to

- Invitation letter?
- Invitation text?
- Invitation phone calls?
- Prompted by Doctor or Nurse testing?

Were other methods used to recruit patients? What were they? Why were they used? Do you think they were successful?

4. Consenting Patients to the Trial

How did you find the consent process (as a staff member)?

On average how long did it take to explain the trial and consent patients?

- What were the patients' reactions to the consent process?
- What were patients' reactions to having a blood test as part of the trial?

Did you personally refer patients to the HepFREE team if they tested positive?

- If yes - could you tell me about the referral process? Was it fairly easy or difficult?
- If no, do you know who did?

5. Other Questions:

Based on your experience of HepFREE which aspects went well?

Which did not go well?

Are there any changes you would suggest?

- For staff
- For patients

On balance, would you be happy to take part in this type of study again?

- Why do you say that?

Would you be happy to screen for viral hepatitis routinely?

- Why do you say that?