Chronic viral hepatitis in ethnic minorities. Strategies to prevent the predicted increase in mortality

NIHR Programme Grant RP-PG-1209-10038

Final study report

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Executive summary

Chronic infection with hepatitis B and hepatitis C viruses leads, over many decades, to cirrhosis and liver cancer in a proportion of those infected. Intervention with antiviral agents in the asymptomatic phase reduces mortality. People born outside England have a higher prevalence of infection than the indigenous population. The purpose of this study was to determine the most effective way to identify, engage and treat migrants with infection to reduce the risk of end-stage liver disease from chronic viral hepatitis.

We completed a qualitative analysis of knowledge of, and attitudes to, viral hepatitis in immigrants. We found limited knowledge and widespread misunderstanding about hepatitis infection.

We completed a cluster randomised controlled trial of screening in general practices in areas of high immigrant density (London and Bradford). This 'screening trial' involved 63 practices and examined the hypothesis that supported screening was more effective than standard of care. In areas with large immigrant communities (Bradford, London) 58 of 63 general practices contributed data on immigrant viral hepatitis screening. Control practices (8) were advised to screen patients opportunistically in line with national guidelines (standard care); intervention practices (50) were provided with screening support, including prompts in medical records and a fee for each test completed. 90,250 patients were eligible for testing and 11,929 were screened. Testing rates were higher in intervention practices (11,386 of 58,512 (19.5%) compared to 543 of 31,738 (1.7%) p=0.014)). The overall prevalence of viral hepatitis in those tested was 2% (1% HBsAg positive, 1% HCV antibody positive). One in three (32%) people with HCV antibodies were viraemic. When we tested, in an embedded cluster randomised trial, 'bespoke' invitation letters compared to 'generic' letters inviting people for testing there was no significant difference in the uptake of screening. We noted differences in screening attendance by age with an increase in both attendance and prevalence in older immigrants.

The 50 practices that had received targetted screening were included in a second trial to determine whether patients identified by screening engaged with clinical care and to examine the benefits of community treatment. We randomised practices to community care with a liver specialist managing patients in community surgeries or standard hospital care. We saw no major benefits from costly community care and engagement was excellent throughout.

In a parallel, observational study we examined the impact of screeing in area of low immigrant diversity (Oxford). Nine general practices were asked to test a total of 6,854 people and were paid for so doing. Testing rates were lower (515 of 6854, 7.5%) than those seen in areas of high immigrant density.

In a cost effectiveness analysis the intervention was cost effective at normal willingness to pay thresholds – using the list price of medication the cost per QALY for screening was £8,450.

Conclusion

Screening for chronic viral hepatitis in immigrant communities is effective if general practitioners are funded for testing and provided with support. This intervention is cost effective and identifies patients with chronic viral hepatitis who engage in antiviral therapy delivered in a hospital setting. Bespoke invitation letters and community care were not advantageous and can not be recommended.

1. Index

2. Index of figures and Table

3. Keywords

Hepatitis B
Hepatitis C
Viral Hepatitis
Immigrants
Screening
Case finding
Prevalence

4. Conflict of interest

Professor Foster has received personal and institutional funds from companies that market drugs for the treatment of chronic viral hepatitis – specifically AbbVie, BMS, Gilead, GSK, Merck

Dr Agarwal has received personal and institutional funds from companies that market drugs for the treatment of chronic viral hepatitis – specifically Arbutus, AbbVie, BMS, Gilead, Merck, VIR

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6. Abbreviations

AE- adverse events
ALT- alanine transaminase
AST- aspartate transaminase
CI- confidence interval
DAA- directly acting antiviral
DMC- Data Monitoring Committee
GP- general practitioner
HBV- hepatitis B virus
HCC- hepatocellular carcinoma
HCV- hepatitis C virus
iu/L- international units per litre
IRR – incidence rate ratio
LFT- liver function test
NHS- National Health Service
NICE- National Institute for Health and Clinical Excellence
NIHR - National Institute for Health and Research
ODN- Operational Delivery Network
OR- odds ratio
p.a.- per annum
PCR- polymerase chain reaction
PHE- Public Health England
PoC- point-of-care
PPI- patient and public involvement
PWID- people who inject drugs
QALY- quality adjusted life year
RCT- randomised controlled trial
SIV – site initiation visit
SVR- sustained virological response
TSC- Trial Steering Committee
ULN- upper limit of normal
WTP- willingness-to-pay

7. Background

7.1 Introduction

Globally, it is estimated that in excess of 500 million people are infected with chronic viral hepatitis B or C (HBV, HCV) [1,2]. The burden of disease associated with viral hepatitis is concentrated in developing countries where transmission of HBV is most often vertical, from mother to child, and transmission of HCV is from unsafe medical procedures and transfusion of unscreened blood products. In developed countries including the United Kingdom (UK), the majority of cases of viral hepatitis arise as a result of injecting drug use (HCV) or sexually (HBV). Multiple initiatives have been developed and implemented in these two latter groups of high-risk individuals to improve screening, diagnosis and treatment of viral hepatitis.

In England, HBV and HCV prevalence is estimated to be less than 0.5% [3,4]. There is uncertainty surrounding this estimate as the unknown prevalence of disease in developing countries, the patterns of migration from high to low-risk countries and the absence of formal screening for viral hepatitis in non-indigenous populations make it difficult to derive accurate estimates. Global patterns of migration favour the movement of individuals from countries with medium or high-risk prevalence of chronic viral hepatitis to countries with traditionally low prevalence, including the UK. In 2015, the United Nations (UN) estimated that 3.3% of the global population were international migrants, posing important implications for healthcare systems in host nations [5]. It is estimated that up to 7 million first and second generation immigrants originating from high prevalence countries now reside permanently in the UK, and this figure is likely to be a conservative estimate of the true volume. Previous studies in migrant populations in developed countries suggested that the prevalence of disease reflects the prevalence in their country of origin [6,7] although UK studies suggest that this is not always the case - Uddin et al studied immigrants in East London and found that the prevalence in immigrants was higher than in the indigenous population but lower than their country of origin [8]. It is probable that immigrants in England who were born outside the country will have a higher prevalence of viral hepatitis, although the magnitude of the increase is unknown.

Chronic infection with viral hepatitis causes progressive liver damage resulting in cirrhosis, with or without the development of hepatocellular carcinoma (HCC). Highly effective therapies are available for the treatment of both HCV and HBV. Sustained virological response (SVR) rates exceed ninety percent in individuals infected with all HCV genotypes and this leads to a rapid reduction in complications from the infection [9]. For chronic HBV infection drugs to suppress viral replication are available and have been shown to reverse liver fibrosis and cirrhosis [10]. Evaluation by The National Institute for Clinical Excellence (NICE) of the drugs for chronic viral hepatitis has shown them to be clinically and cost effective and these therapies are now in widespread use, both in the UK and globally. In England drugs for chronic HCV infection have been made available through operational delivery networks who are charged with prioritising patients and ensuring that a fixed quota of patients are treated every year, in line with NICE estimates of the numbers needing therapy. Although initially the number of treatments available to each network acted as a barrier to treatment access and led to waiting lists for treatment for patients with mild disease the latest data from NHSE (GR Foster – personal communication) indicates that, for most regions, treatment capacity now exceeds registered patients and the national focus is on identification and treatment of new patients. NHSE has indicated its commitment to reducing the burden of disease from chronic HCV infection and strategies to increase testing and identification of infected patients are now under way. Given the high prevalence of viral hepatitis in immigrant communities and the availability of effective treatments, screening for viral liver disease in immigrants is an attractive proposition and NICE guidance on testing for liver disease, recommends that immigrants are offered testing for HBV and HCV. However, the optimal way to screen immigrants for viral hepatitis has not been studied and the cost effectiveness of testing in primary care has not been evaluated. The purpose of this study (HepFREE) was to address the value of screening for viral hepatitis in immigrants in the UK and

to determine the most appropriate testing strategy as well as the clinical and cost effectiveness of this approach. The study involved a preliminary phase of qualitative work examining attitudes to testing 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.

7.2 The study

The 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.

7.3 The trials

A first trial tested the impact of screening for viral hepatitis in immigrants in General Practices (GP) in four areas of England. 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. HepFREE1 commenced screening in Bradford, East London and South London in March 2014. Through targeted screening in high-risk immigrant populations we aimed to determine the optimal approach to screening in immigrant communities and to establish the likely uptake of screening and its cost effectiveness. The study also provided an opportunity to establish the demography of viral hepatitis in immigrant communities living in England.

Screening for a disease, whilst worthwhile, is not an end in itself and control of viraemia and engagement with clinical care is required to achieve the full benefits of case identification. To 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.

Immigrants in England tend to live in inner city locations and their communities are often concentrated in defined geographical areas. However, with increasing integration and mobility more and more immigrants are moving from the traditional immigrant locations to other regions. In regions with small numbers of immigrants the cost-benefits and compliance with testing may be very different from testing in areas of high immigrant density and any national screening programme will require information on testing both in areas of high and low immigrant density. We therefore included an additional site (rural Oxford) in a linked study (HepFREE2) which began in 2015. The site was chosen for its low population of immigrants and served as a comparator to the inner city sites with a high density of people born outside the United Kingdom.

7.4 Aims and objectives

The main aims of the study 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.
8) To determine whether testing for viral hepatitis in a low prevalence setting was equivalent to screening in an area of high prevalence as assessed by proportion of patients attending for testing

Aims 1-3 were addressed with a qualitative study and aims 4 to 7 were addressed in a cluster randomised trial (see below). Aim 8 was determined through a second study (HepFREE2) conducted in Oxford.

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

Primary Objectives

Trial 1

- To determine whether interventional screening is more cost-effective than control screening in the detection of viral hepatitis in ethnic minority patients in primary care.
- To determine the screening rate of intervention practices compared to the screening rate in control GP practices
- To determine whether the provision of an enhanced patient information invitation letters increases attendance for testing when compared to standard information invitation letter

Trial 2

- To determine whether community based therapy is superior to conventional delivery of treatment (based on referral to local hospital treatment centres) as measured by engagement with management).

Secondary Objectives

- To determine the range and prevalence of different beliefs, attitudes and barriers to screening.
- To assess the impact of contextual variables and demographics as well as health literacy in the uptake rate of screening and subsequent treatment engagement.
- To assess treatment adherence between patient groups receiving treatment within the community care setting against standard hospital care.
- To determine the cost effectiveness of the interventions
- To determine the prevalence of viral hepatitis in different ethnic groups living in the UK
- 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 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 attend for testing

- The proportion of potential participants that engage in therapy in the different treatment arms. Engagement is defined as:
    - Attending for the required investigations (3 tests)
    - 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 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 one visit after the management plan has been agreed by the participant and the clinicians
- 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.

7.5 Funding, ethics and governance

HepFREE was funded by the NIHR through the Programme Grants for Applied Research. The study protocol was approved by the NRES Committee London – Fulham on 24 December 2012, REC reference number 12/LO/1768

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 trial steering committee was chaired by Prof William Irving (Chairman), supported by Dr Moira Kelly and Dr Alan Montgomery

7.6 Pre-trial assessment – literature review, assessment of community needs and development of a patient information letter.

Prior to the introduction of screening in general practices we conducted a literature review of knowledge and attitudes to hepatitis B and C among immigrants and refugees followed by a qualitative study of at-risk immigrants and healthcare professionals. The output from these studies has been published [11,12]. Our systematic review involved an inclusive search of seven electronic databases (PubMed, CINHAL, SOCIOFILE, PsycINFO, Web of Science databases (Science Citation Index Expanded (1970-present) Social Sciences Citation Index (1970-present), Arts & Humanities Citation Index (1975-present), Conference Proceedings Citation Index- Science (1990-present), Conference Proceedings Citation Index- Social Science & Humanities (1990-present)) and identified a total of 51 publications. However the majority of papers included small samples with heterogenous methods and outcomes and focussed, predominantly, on hepatitis B. The majority of studies involved South East Asians in the USA, Canada and Australia and we found very little research on immigrants from other areas with high prevalence of HBV and HCV infections, such as Central Asian republics, South Asia, Africa, Middle East, and Eastern Europe.

The literature indicated that many immigrants lacked adequate knowledge of aetiology, symptoms, transmission risk factors, prevention strategies and treatment of viral hepatitis. Ethnicity, gender, better education, higher income, and English proficiency influenced variations in levels and forms of knowledge. Of importance, most studies indicated that participants associated viral hepatitis (chiefly HBV) with 'yellow symptoms' and knowledge of the asymptomatic nature of the infection was sparse. Knowledge of the routes of transmission of viral hepatitis was patchy with some South East Asian participants recognising the sexual nature of HBV transmission but many participants attributing transmission of HBV infection to factors such as contaminated and uncooked or poorly cooked food and communal sharing of food and drinks. Surveys showed that between 21% and 71% of participants believed that HBV infection could be transmitted through eating of food prepared by an infected person, and between 26% to 48% of the Chinese participants 'knew' that HBV infection could be transmitted through sharing of food and drinks. Between 34% and 91% of participants in surveys knew of the vertical transmission of HBV infection through child birth and there was evidence of knowledge of transmission of HBV through contaminated (therapeutic) injection practices. The proportion of survey participants who knew of this risk factor varied between studies from 18% to 92%. For HCV infection some immigrants were aware of association with contaminated injecting drug paraphernalia. The impact of HBV and HCV was often recognised with a sizable proportion of individuals recognising that infection could lead to cirrhosis and cancer. Knowledge of treatments was generally poor.

To complement and expand the literature review we completed a qualitative study of at-risk immigrant communities and healthcare professionals. We collected qualitative data in three sequential phases- (i) semi-structured interviews with key informants *(n = 17)*, (ii) focus groups with people from Chinese, Pakistani, Roma, Somali, and French- and English-speaking African communities *(n = 95)*, and (iii) semi-structured interviews with general practitioners working in areas with a high prevalence of migrants at risk of viral hepatitis *(n = 6)*. Datasets from each phase were analysed using the Framework method. We found that our informants and general practitioners perceived that there was limited knowledge and understanding about hepatitis B and C within high-risk immigrant communities, and that chronic viral hepatitis did not typically feature in community discourses about serious illness. Many focus group participants were confused about the differences between types of viral hepatitis, held misconceptions regarding transmission, and were unaware of the asymptomatic nature of chronic infection. Most welcomed the idea of a screening programme, but key informants and focus group participants also identified numerous practical barriers to engagement with primary care-based screening and treatment; including language and communication difficulties, limited time (due to long working hours), and (for some) low levels of trust and confidence in general practice-based care. General practitioners expressed concerns about

the workload implications and sustainability of screening and treating immigrant patients for chronic viral hepatitis in primary care.

Our literature review and focus group analysis identified common themes among immigrant communities. There was limited knowledge of viral hepatitis and, of particular concern, there was little understanding of the asymptomatic nature of the infections and considerable misunderstanding of the routes of transmission. Information campaigns to address these concerns are likely to be required to improve awareness of viral hepatitis in immigrant communities.

7.7 Development of an introductory letter to patients

To inform patients of the screening trial and to alert them to the issues around viral hepatitis we agreed to send prospective trial participants a letter informing them of the trial. To determine whether a targeted information letter specific for the ethnic group in question and based on the learnings from our qualitative work is more effective than a generic letter we randomised practices to an 'enhanced' or 'standard' invitation letter (See later for details of the randomisation). The enhanced letters were prepared by the study team, discussed with a patient focus group and then submitted for approval by an appropriately constituted ethics committee. The test of the letters is provided in Appendix 2

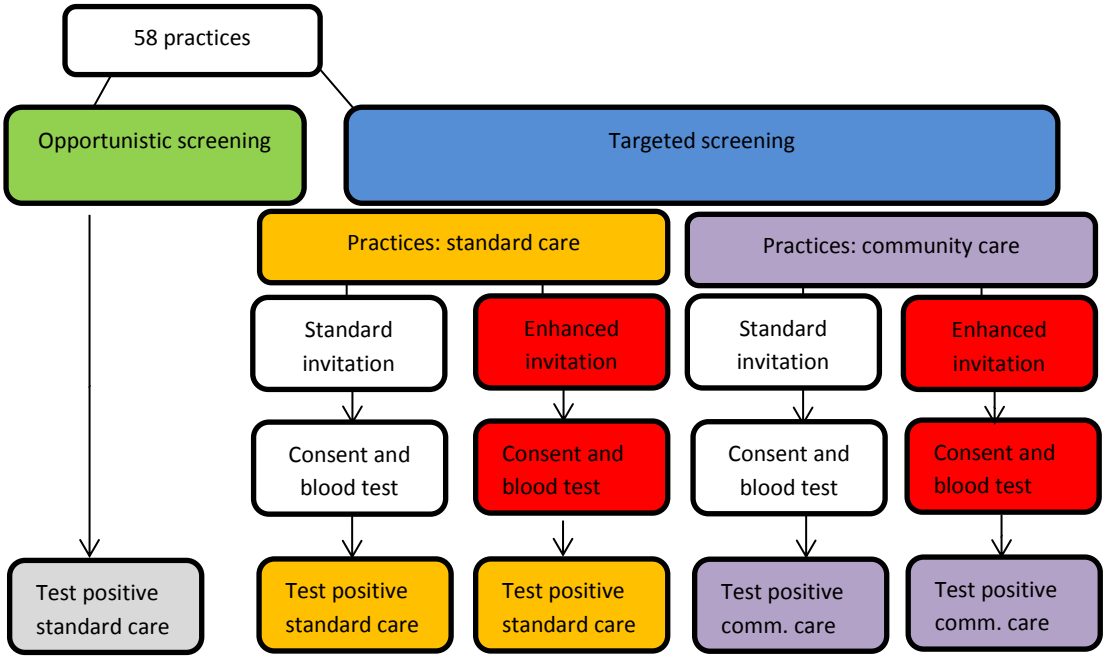
8. HepFREE1

HepFREE1 was a study comprising two cluster randomised controlled trials conducted in GP practices in three areas of England: north-east London, south-east London and Bradford. The first trial (a 'screening trial') was designed to invite up to 48,000 eligible participants from fifty GP practices that had been recruited to participate and subsequently randomised to the intervention arm of the trial. A further eight practices were recruited and assigned to the control arm of the trial. The eight practices randomised and assigned to the control arm provided information on testing rates and subsequent engagement with treatment in a further 4,000 individuals. An embedded study randomized practices in the targeted screening arm to 'augmented' invitation letters or 'standard' letters. Eighteen out of the fifty practices were assigned to the intervention arm that sent a simplified 'standard' invitation letter to all eligible participants, and the remaining thirty-two invited participants used the 'augmented' trial invitation letter.

A second trial (the 'treatment trial'), nested in the first trial, randomised practices in the targeted screening arm of the first trial 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.

Trial randomisation was performed using the method of minimisation. The programme managing allocations was web-based, and developed using Java at Queen Mary University London. Figure 1 illustrates the study design.

Figure 1 Overview of the trial design



The first trial was a cluster randomised trial of screening. Therefore, there was no individual participant consent to participation. Participants gave 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 second 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.

- Comparison of screening results in control and intervention practices, coloured green and blue respectively will investigate hypothesis one (in trial 1), that targeted screening for viral hepatitis in first and second generation immigrants in primary care is superior to opportunistic screening in identifying patients with viral liver disease.
- Comparison of the screening outcomes in practices inviting eligible individuals using the enhanced invitation with outcomes in practices using the standard invitation letter, coloured red and white respectively on the flow diagram will investigate hypothesis two, that providing additional information on the condition of viral hepatitis encourages individuals to enroll in the study and take up the offer of a screening blood test.
- Comparison of the engagement and treatment outcomes in participants receiving standard of care versus care in the community (in trial 2); coloured orange and purple on the flow chart respectively will investigate hypothesis three, that providing additional information on the condition of viral hepatitis encourages individuals to enroll in the study and take up the offer of a screening blood test.

The protocol for the trial is included in Appendix 1 along with the protocol amendments. The most significant change to the protocol occurred In August 2014 (Protocol version 6). When the trial

was initiated pilot studies indicated that each general practice was likely to enrol approximately 500 patients. Between proposal and trial initiation, changes in general practices, 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 proposed number of practices would have led to enrolment of over 100,000 patients –i.e. a doubling of the trial size. Given that this was 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 practice (35) should be 'capped' and recruitment should only involve a total of 500 patients. However, to determine whether recruitment of all patients from a practice was feasible 15 practices that had initiated recruitment prior to the amendment continued to recruit all patients. Thirty five practices were capped at a total recruitment of 500 patients. 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 see the total number of patients that fit 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.

8.1 Trial methodology HepFREE1

8.1.1 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 that 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.

8.1.2 The targeted screening (intervention) arms

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 previous).

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 participants 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.

8.1.3 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 1 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

8.1.4 Eligibility criteria – inclusion and exclusion 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 end of the protocol – appendix 1).
- 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. For 'uncapped practices' with no limit on the number of patients to be tested, patients who newly registered with the practice during the study period and who were eligible for enrollment were considered for testing and we encouraged testing of such patients.

Criteria for exclusion were age <18 years. Patients who were unable to consent to the testing procedure were not tested. Patients were allowed to withdraw from the trial at any time and data up to the time of withdrawal was retained and analysed.

8.1.5 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 (CSUand 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 a limited number of uncapped intervention practices (four) data was collected on additional invitations by text and phone call to assess the amount of extra patient contact that was required from admin staff for each successfully recruited individual.

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

Systm One 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 patients 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.

8.1.6 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.

8.1.7 Management of patients at screening

For patients identified as eligible for the study an invitation letter was sent inviting attendance and participation in the trial. In addition 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 asked to participate if they attended the surgery for another reason. Patients were asked for consent to take blood and use the results in the trial when they responded to the letter or when they were invited to participate at an attendance visit. 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). Samples were tested for anti-HCV using the Abbott ARCHITECT Anti-HCV assay (Abbott Laboratories. Abbott Park, Illinois, U.S.A.). If the result obtained from the ARCHITECT anti-HCV test was positive, the sample was referred for confirmatory testing using the Diasorin Liason XL assay (Via Crescentino snc - 13040 Saluggia (VC)). This test also uses CMIA technology for qualitative detection of anti-HCV. If there was a discrepancy in the results

obtained from the first and second tests, a third test was performed on samples using the Orthogenics HCV antibody kit.

HepFREE study samples were tested and reported as follows

Anti-HCV positive - automatically referred for RNA testing using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, Roche Molecular Diagnostics (4300 Hacienda Drive, Pleasanton, CA 94588, USA) and results reported to the referring GP

Anti-HCV negative - the screening test for HCV was negative and reported to the referring GP

Low level anti-HCV - 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.

HBsAg - tested using the Abbott ARCHITECT HBsAg qualitative assay. 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.

All participants were informed of their result by their GP at a subsequent attendance at the practice.

8.1.8 Management of patients identified with chronic viral hepatitis and individual consent for participation in second 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. The trial clinical fellow was informed of the result and was responsible for generating a referral for the participant to attend secondary care. The participant was notified of this appointment by a letter to their home address and text message reminder. Irrespective of the randomisation outcome regarding location of treatment services, all participants had their initial diagnostic assessment performed in secondary care. At the out-patient appointment a member of the study team, blinded to the randomisation schedule, discussed the results and sought consent for participation in the second trial involving either standard or community care. The participant was informed that if they chose to continue in the trial they would be randomised to receive treatment for viral hepatitis if required, and would be invited to attend all subsequent follow up appointments either in hospital (standard care) or in the community. Prior to giving consent, participants were provided with a further information leaflet which outlined the nature of the second 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.

8.1.9 Community treatment in HepFREE

Community treatment was provided at two GP surgeries in Bradford, three in NE London and four in SE London. Practices were reimbursed for the number of hours the practice room was used by a member of the research team. Establishing community treatment services proved challenging and required significantly more input than originally envisaged.

8.1.10 Hospital treatment in HepFREE

For patients randomised to hospital based care standard procedures were used whereby patients were seen in the hospital out-patient clinic in accordance with standard hospital management guidelines.

8.1.11 Treatments offered

All patients with chronic HCV infection underwent an assessment of the degree of liver fibrosis (either by liver biopsy of fibroscan) and were offered treatment in accordance with NHSE and NICE guidelines. From initiation of screening the first group of intervention practices in March 2014 until September 2016, therapy 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 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.

All patients with chronic HBV infection were assessed for the degree of disease activity in line with standard practice and those with active disease were offered therapy with third generation antiviral agents – either entecavir or tenofovir.

8.1.12 Data collection

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

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

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 and calculation of APRI)
- 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

Trial 2

For patients who tested positive data was collected on

- Attendance for fibrotic assessment
- HCV and HBV disease assessment
- Treatment assessment appointments

Compliance with anti-viral treatment was assessed by treated efficacy measured after 12 weeks and following antiviral therapy for hepatitis C at 12 weeks after cessation of therapy. These data were collected from electronic health records and entered directly onto the OpenClinica database developed by the PCTU data management team. Data on clinical engagement was collected by the clinical fellow from entries in the medical records

8.1.13 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 in Data Capture section 8.1.12

Initial data cleaning was undertaken by a data manager and 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.

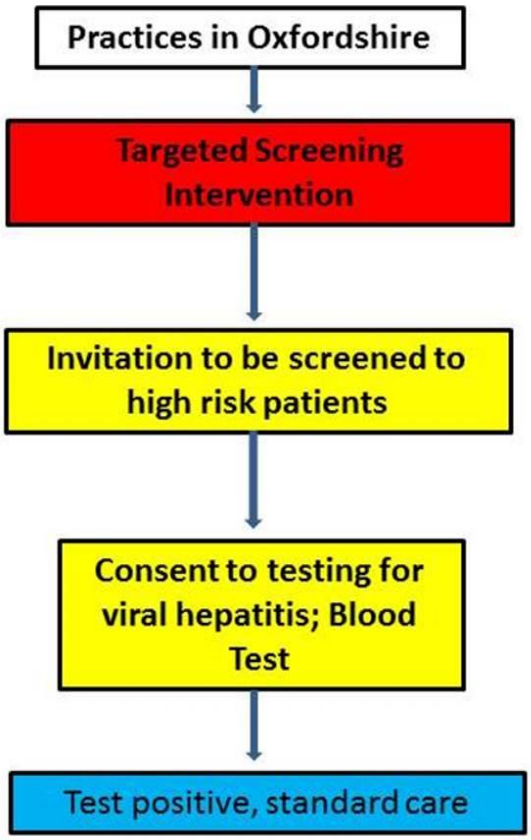
Final cumulative reports of eligible patients from SystmOne practices, from uncapped EMIS practices and from capped EMIS practices were produced. A final cumulative screening report for SystmOne and for EMIS practices was also produced and cross referenced with the eligibility reports to produce a final 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.

9. HepFREE 2

HepFREE2 was an observational study to determine how to effectively identify and screen immigrants from "at risk" ethnic minority communities for viral hepatitis in areas of low immigrant prevalence. The same targeted screening approach used in the main HepFREE trial (i.e. identification and testing of all consents adult patients from at-risk populations) was used at nine GP practices in Oxfordshire over an 18 month period, inviting ~5,000 eligible participants. The protocol for the trial is included in Appendix 1 with the protocol amendment log in Appendix 2. The trial overview is shown in Figure 2

Figure 2 Overview of the HepFree2 Study Design



The most substantial amendment to the protocol occurred In September 2016 (Protocol version 4). When this observational study was initiated a study pilot indicated that each general practice was likely to invite approximately 50 eligible patients, and preparations were made to engage up to 24 GP practices. However eligibility reports suggested each practice was likely invite 400 eligible patients. Therefore the number of practices involved was reduced from 24 to 8.

9.1 Trial methodology HepFREE2

9.1.1 Eligibility criteria - inclusion and exclusion criteria

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

- Originated from a country with a prevalence of viral hepatitis of more than 2% (List of countries available in 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 anyone that had previously been involved in a HBV immunisation programme. All practices were 'uncapped' with no limit on the number of patients to be tested, patients who newly registered with the practice during the study period and who were eligible for enrollment were considered for testing and we encouraged testing of such patients. Criteria for exclusion were age <18 years. Patients who were unable to consent to the testing procedure were not tested. Patients were allowed to withdraw from the trial at any time and data up to the time of withdrawal was retained and analysed. Note that the eligibility criteria were identical to those for HepFREE1.

9.1.2 Patient selection

First and second generation immigrants from known 'at risk' communities (See Protocol - Appendix) were identified utilising GP practice list definitions of ethnicity. Patients were contacted either by letter, text message or opportunistically when visiting the GP. In all circumstances the patient was given written information and time to consider whether or not they wish to be tested and provide data for the study. Patients could choose to re-attend the practice at a later date to confirm participation. Written Informed Consent was taken from the patient prior to the blood test. Patients were then tested using standard local testing approaches at either onsite practice phlebotomy services or via onward referral to local phlebotomy services. If tested positive for viral hepatitis, patients were invited to re-attend the GP to receive their result and managed by referral to hospital, as per standard practice. This approach mirrored the approach used in HepFREE1

9.2 HepFree2 Study Procedure Overview

In nine practices, existing GP registers of patients were screened to identify prospective patients by recorded ethnicity, country of birth or their parents' country of birth and first language spoken. Potential participants for screening were approached and invited for testing for viral hepatitis, via letter which included a copy of the patient information sheet and informed consent form attached (in English or appropriate translation, if applicable). This explained the details of the processes relating to screening and what happens should they test positive for viral hepatitis.

First/second generation immigrants were considered for the study and all those screened and testing positive for viral hepatitis were referred for ongoing care and any treatment in the specialist outpatients clinic in a local hospital. Patients who tested positive for viral hepatitis were monitored for their level of engagement as well as treatment compliance as a secondary study outcome. Engagement was measured relating to the patient's attendance and we defined 'engaged' as attending for three visits after receiving their positive result over the first 12 months. If patients attended for blood tests and are found to be HCV Ag positive but HCV RNA negative on two separate occasions, they were included and considered to have "engaged" with the study. Attendance within the first 12 months of diagnosis was captured to ascertain if the patient was engaged and compliant with their care and treatment. Patients who undergo therapy will be assessed for compliance by confirmation – treatment compliance being defined as taking more than 80% of the prescribed medication.

Patients received their standard local hospital care upon referral from the practices, in which local consultant physicians will manage their treatment and monitoring in line with current practice.

9.2.1 Data capture

All Oxford practices used the EMIS web system and therefore the CEG trial-specific template was designed by CEG was used for data capture. The template was used to collect and record specific trial-related activities using Read codes.

9.2.2 Management of patients at screening

Patients were asked for consent to take blood and use results when they responded to the trial invitation letter or when they were invited to participate at an attendance visit. Following informed consent six millilitres of venous blood was obtained by venepuncture and sent in a Serum Clot Activator VACUETTE® sample tube with a study specific proforma requesting for the sample to be tested for HBsAg and anti-HCV to the local virology laboratory Blood samples were sent to local virology laboratories for analysis. Blood samples were analysed forHBsAg and HCV Ag per local protocols as part of the screening process. GP practices and local virology laboratory teams liaised closely to ensure that participants received their result, as per standard practice. GPs made the virology team aware of patients that consented to the HepFREE trial. As the screening outcome directly relates to the primary objective of this study, the HepFREE research team liaised with both the GP practices and virology laboratories to ensure that screening outcome was captured accurately for participants. The identity of the participants were not disclosed to the HepFREE research team and the screening results were linked to an anonymised number.

10. Trial definitions, analyses and power calculations – HepFREE1 and HepFREE2

10.1 Trial definitions

Trial 1 ('Screening trial') Screening rates: standard screening vs interventional screening (8 v 48 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 are invited, the number deemed eligible is 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 will be 500).
Numerator – number of patients attending a blood test and for whom the GP practice has received their results over the 18 months trial period.

Trial embedded in trial 1: Screening rates: standard invitation letter vs enhanced invitation letter (24 v 24 practices)
Denominator – the number of individuals deemed eligible to be screened at each GP practice over the 18 months screening period. (In interventional screening practices where all eligible individuals are invited, the number deemed eligible is the number of individuals fulfilling the eligibility criteria over the 18 months screening period. In intervention practices where only 500 individuals were randomly selected for inviting, the denominator will be 500).
Numerator – number of patients attending a blood test within 31 days of the date at which the invitation letter was sent and for whom the GP practice has received their results over the 18 months trial period.
Trial 2 ('Treatment trial') Engagement rates (binary outcome): community care vs standard care
Numerator – number of patients engaged with clinical assessment. 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

Denominator – number of patients tested positive for viral hepatitis. Patients tested positive, but do not come to receive their results after contacting them on three separate occasions are recorded as 'not-engaged'.
Numerator – number of patients attending the three scheduled treatment visits or for patients who are antibody positive or for patients who are HCV antibody positive or equivocal but HCV RNA negative, attending the GP practice or the local hospital on two separate occasions for managing hepatitis treatment.
The proportion of patients that are compliant with their prescribed clinical management plan in the different treatment arms (community care Vs Standard hospital care).
Trial 2 Compliance rates: community vs standard care
Compliance with the clinical management plan is defined as attending at least 1 visit within 6 months after the management plan has been agreed by the participant and the clinicians
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.
Secondary outcomes
Trial 1 - 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
Trial 1 - 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
Trial 1 - Screening rates in new registrants for viral hepatitis (only applicable for practices offering 'unrestricted' 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).
Trial 2: Adherence to anti-viral therapy
Denominator – number of patients went on to have at-least one dose of anti-viral therapy
Numerator – number of patients completing at least 80% or more of their prescribed antiviral treatment
Trial 2 Sustained viral response
For patients with hepatitis a sustained virological response (SVR) is defined as undetectable HCV RNA (i.e. viral load below 18IU/ml) 12 weeks after treatment completion for hepatitis C patients. The definition of sustained viral response for hepatitis B treatment is a reduction in viral load to <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 SVR12 or SAV24 based on what anti-viral treatment the patient is on for Hepatitis C. For Hepatitis B, 80% reduction in viral load 12 weeks into the treatment

10.2 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 (ie 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.

10.3 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 and three in trial 2. 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 trial 2,

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.

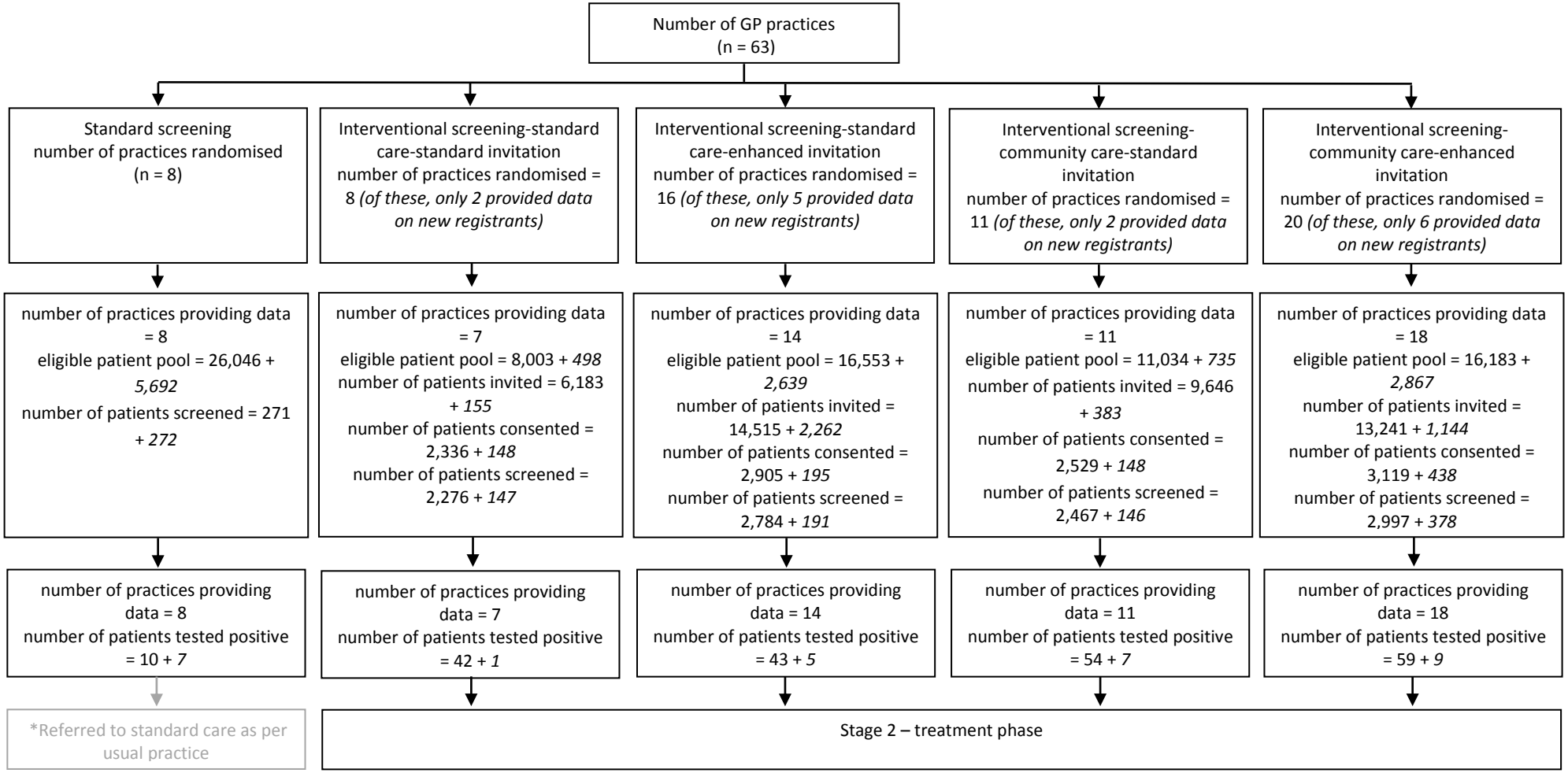
11. HepFREE1 - Results

The study overview and CONSORT flowchart are shown in Figure 3.

11.1 Patient and practice characteristics

A total of 63 practices originally agreed to participate in the study and their characteristics are shown in Table 4. Five practices withdrew from the study before contributing any data and the details of the 58 practices who provided data for the study are shown in Table 5.
The characteristics of all of the patients involved in the study are shown in Table 6a. A large number of patients registered with the study practices over the course of the study and the characteristics of the original and new registrants are shown in Tables 6b and c respectively.

Figure 3 CONSORT overview of the study



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

**Number of new registrants are provided in italic*

Table 2 Characteristics of practices agreeing to participate

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 3 Characteristics of 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 Tables 4a,b and c. A total of 90,250 participants in 58 practices were included in trial 1, 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 we 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

Table 4a 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 4b Characteristics of participants registered with study practices at the start of trial 1 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 4c 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)

11.2 Trial 1: 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 5a, 5b and 5c show the characteristics of these participants.

Table 5a 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 5b Characteristics of eligible, invited, and screened participants registered with study practices at the start of trial 1 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 5c Characteristics of eligible, invited, and screened participants who joined the study 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 6a, 6b, 6c. 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 6a 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 6b 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 6c 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 7a)

7a: 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 7b: 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 8a outlines the demographics of the patients and Table 8b details the analysis. There was no significant difference in screening rates with the two different letters.

Table 8a: Screening rates: standard invitation vs enhanced invitation – demographics

Patient characteristics	Standard invitation (number of practices = 18)						Enhanced invitation (number of practices = 32)					
	Eligible patient pool (n = 19,037)		Invited for screening (n = 15,844)		Screened within 31 days of invitation letter been sent (n = 720)		Eligible patient pool (n = 32,736)		Invited for screening (n = 28,095)		Screened within 31 days of invitation letter been sent (n = 1,032)	
	No	%	No	%	No	%	No	%	No	%	No	%
Gender												
Female	9,524	50.0%	7,923	50.0%	394	54.7%	17,024	52.0%	14,381	51.2%	622	60.3%
Male	9,513	50.0%	7,921	50.0%	326	45.3%	15,711	48.0%	13,713	48.8%	409	39.6%
Missing	-	-	-	-	-	-	1	0.0%	1	0.0%	1	0.1%
Ethnicity												
Black	2,727	14.3%	2,576	16.3%	22	3.1%	3,723	11.4%	3,300	11.7%	44	4.3%
Bangladeshi	1,480	7.8%	1,367	8.6%	68	9.4%	1,668	5.1%	1,458	5.2%	55	5.3%
Indian	957	5.0%	756	4.8%	100	13.9%	3,986	12.2%	3,520	12.5%	115	11.1%
Pakistani	7,215	37.9%	5,403	34.1%	460	63.9%	10,482	32.0%	9,302	33.1%	611	59.2%
Other Asian	1,011	5.3%	843	5.3%	11	1.5%	2,898	8.9%	2,348	8.4%	56	5.4%
Eastern	501	2.6%	350	2.2%	6	0.8%	1,930	5.9%	1,520	5.4%	48	4.7%
Other	5,146	27.0%	4,549	28.7%	53	7.4%	8,049	24.6%	6,647	23.7%	103	10.0%
Age (years)												
mean (sd)	39.8 (15.4)		40.3 (15.4)		45.7 (16.3)		38.9 (14.7)		39.1 (14.8)		44.9 (15.5)	

Table 8b: Screening rates: standard invitation vs enhanced invitation – analysis

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

Intracluster Correlation Coefficients = 0.057 (95% CI: 0.035 to 0.078)

11.3 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 9a. The prevalence in those originally registered with the practice and those who registered during the study is shown in Tables 9b and c respectively.

Table 9a Estimated 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 – prevalaence in those <39 years old was 1.95% compared to 2.06% in older patients

Table 9b Prevalence of infection in patients registered with study practices at the start of trial 1

	Standard screening							Interventional screening							
		Total tested positive		HBsAg + ve		HCV antibody + ve			Total tested positive		HBsAg + ve		HCV antibody + ve		HCV RNA + ve	
	No. screened	No.	% of screened	No	% of screened	No	% of screened	No. screened	No	% of screened	No	% of screened	No	% of screened	No	% of screened
Total	271	10	3.7%	7	2.58%	3	1.11%	10,524	198	1.9%	10	0.96%	98	0.93%	34	0.32%
Ethnicity																
Black	67	3	4.5%	2	2.99%	1	1.49%	537	8	1.5%	7	1.30%	1	0.19%	0	0.00%
Bangladeshi	47	2	4.3%	2	4.26%	0	0.00%	821	11	1.3%	8	0.97%	3	0.37%	0	0.00%
Indian	13	0	0.0%	0	0.00%	0	0.00%	1,024	9	0.9%	5	0.49%	4	0.39%	2	0.20%
Pakistani	24	2	8.3%	0	0.00%	2	8.33%	6,414	128	2.0%	48	0.75%	80	1.25%	30	0.47%
Other Asian	28	0	0.0%	0	0.00%	0	0.00%	324	8	2.5%	8	2.47%	0	0.00%	0	0.00%
Eastern Caucasian	1	1	100.0%	1	100.00%	0	0.00%	306	8	2.6%	5	1.63%	4	1.31%	2	0.65%
Other	91	2	2.2%	2	2.20%	0	0.00%	1,098	26	2.4%	20	1.82%	6	0.55%	0	0.00%
Gender																
Female	142	5	3.5%	2	1.41%	3	2.11%	6,059	85	1.4%	32	0.53%	53	0.87%	20	0.33%
Male	129	5	3.9%	5	3.88%	0	0.0%	4,464	113	2.5%	69	1.55%	45	1.01%	14	0.31%
Missing	0	0	0.0%	0	0.00%	0	0.0%	1	0	0.0%	0	0.00%	0	0.00%	0	0.00%
Age group																
18-19	6	0	0.0%	0	0.00%	0	0.00%	223	0	0.0%	0	0.00%	0	0.00%	0	0.00%
20-29	56	2	3.6%	2	3.57%	0	0.00%	1,765	15	0.9%	10	0.57%	5	0.28%	4	0.23%
30-39	94	4	4.3%	4	4.26%	0	0.00%	2,631	55	2.1%	22	0.84%	33	1.25%	15	0.57%
40-49	66	2	3.0%	0	0.00%	2	3.03%	2,451	61	2.5%	32	1.31%	29	1.18%	7	0.29%
50-59	30	2	6.7%	1	3.33%	1	3.33%	1,606	34	2.1%	17	1.06%	17	1.06%	5	0.31%
60-69	16	0	0.0%	0	0.00%	0	0.00%	1,082	22	2.0%	15	1.39%	8	0.74%	1	0.09%
70-79	1	0	0.0%	0	0.00%	0	0.00%	558	8	1.4%	4	0.72%	4	0.72%	1	0.18%
80-89	2	0	0.0%	0	0.00%	0	0.00%	197	3	1.5%	1	0.51%	2	1.02%	1	0.51%
90-99	0	0	0.0%	0	0.00%	0	0.00%	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	0.0%	0	0.00%	0	0.00%	0	0.00%

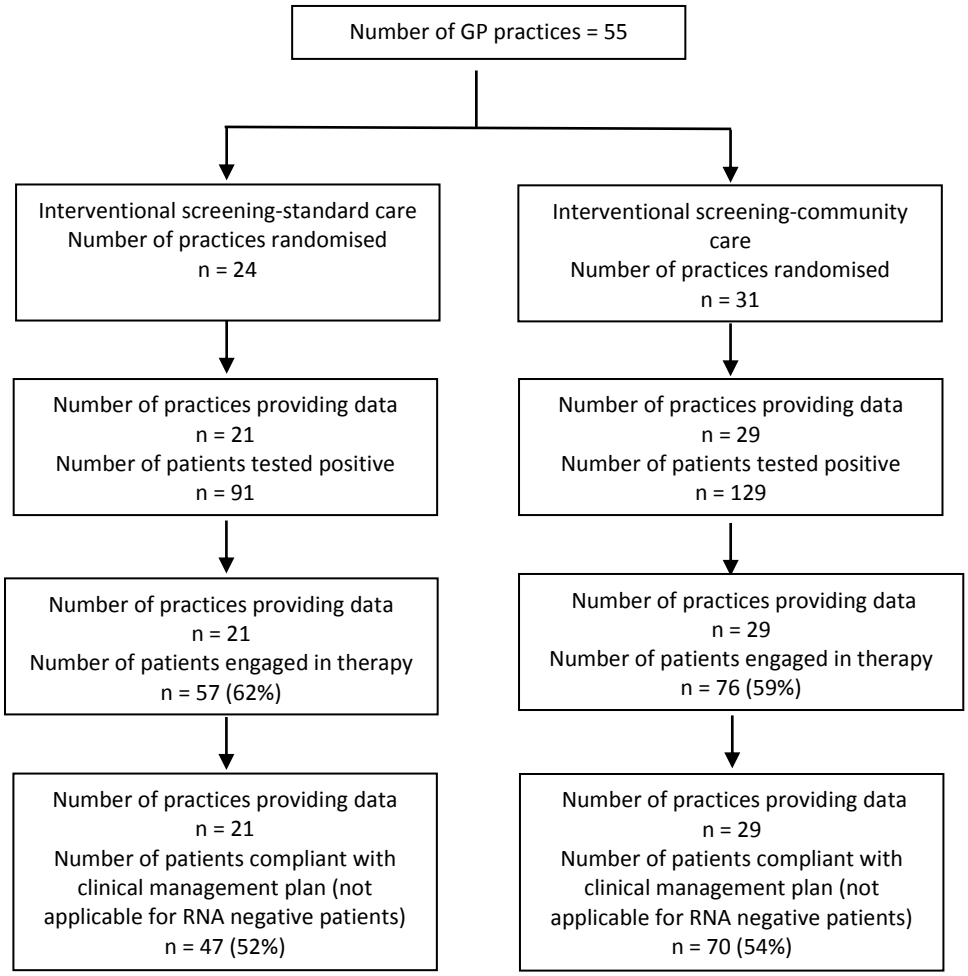
Table 9c Prevalence of infection in patients screened who joined the study during the study period

	Standard screening							Interventional screening							
		Total tested positive		HBsAg + ve		HCV antibody + ve		No. of patients screened	Total tested positive		HBsAg + ve		HCV antibody + ve		HCV RNA + ve	
	Number of patients screened	No.	% of screened	No.	% of screened	No	% of screened		No.	% of screened	No.	% of screened	No.	% of screened	No.	% of screened
Total	272	7	2.6%	5	1.84%	2	0.74%	862	22	2.60%	14	1.62%	8	0.93%	2	0.23%
Ethnicity																
Black	45	0	0.0%	0	0.00%	0	0.00%	8	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Bangladeshi	14	0	0.0%	0	0.00%	0	0.00%	84	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Indian	12	0	0.0%	0	0.00%	0	0.00%	124	2	1.60%	2	1.61%	0	0.00%	0	0.00%
Pakistani	14	2	14.3%	2	14.29%	0	0.00%	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	0.00%	0	0.00%
Eastern	8	0	0.0%	0	0.00%	0	0.00%	100	2	2.00%	2	2.00%	0	0.00%	0	0.00%
Other	152	3	2.0%	2	1.32%	1	0.66%	120	6	5.00%	5	4.17%	1	0.83%	0	0.00%
Gender																
Female	162	4	2.5%	2	1.23%	2	1.23%	478	10	2.10%	5	1.05%	5	1.05%	0	0.00%
Male	110	3	2.7%	3	2.73%	0	0.00%	384	12	3.10%	9	2.34%	3	0.78%	2	0.52%
Age group																
18-19	0	0	0.0%	0	0.00%	0	0.00%	0	0	0.00%	0	0.00%	0	0.00%	0	0.00%
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	0.00%	0	0.00%	155	3	1.90%	0	0.00%	3	1.94%	0	0.00%
50-59	8	0	0.0%	0	0.00%	0	0.00%	97	3	3.10%	2	2.06%	1	1.03%	0	0.00%
60-69	1	0	0.0%	0	0.00%	0	0.00%	48	2	4.20%	2	4.17%	0	0.00%	0	0.00%
70-79	1	0	0.0%	0	0.00%	0	0.00%	21	2	9.50%	1	4.76%	1	4.76%	0	0.00%
80-89	0	0	0.0%	0	0.00%	0	0.00%	9	0	0.00%	0	0.00%	0	0.00%	0	0.00%
90-99	0	0	0.0%	0	0.00%	0	0.00%	0	0	0.00%	0	0.00%	0	0.00%	0	0.00%
100 and over	0	0	0.0%	0	0.00%	0	0.00%	0	0	0.00%	0	0.00%	0	0.00%	0	0.00%

11.4 Trial 2: Engagement in care

To determine the level of engagement in further diagnostic procedures and compliance with therapy we compared patients from practices allocated to 'standard care' and 'community care'. The CONSORT diagram is shown in Figure 4. Setting up community care in primary care centres proved problematic and there were very significant delays in establishing appropriate treatment centres. For some patients who tested positive in the early months of the trial, participation in 'community care' was not immediately available and these patients defaulted to hospital care. It was noteworthy that patients did not regard community care as sufficient justification to delay initiating treatment. A further cohort of patients allocated to community care withdrew consent and reverted to hospital based care (see Methods for details of the consent process for this phase of the study) further reducing the number of participants. To analyse this study we completed a conservative 'intent to treat' analysis and, because of the unanticipated numbers of participants who did receive treatment as intended, a post hoc analysis documenting the 'per-protocol' engagement.

Figure 4 CONSORT flow chart from trial 2.



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

The patient demographics for this intent to treat analysis are shown in Table 10 and Table 11 documents engagement and compliance. There was no significant difference between the two

treatment arms as shown in Tables 12 and 13. Table 15 shows engagement and Table 16 shows compliance with clinical management plan - community care vs standard care (defined as the proportion of patients attending at least one visit within 6 months, after the management plan was agreed by patient and clinician)

Table 10: Characteristics of eligible participants for trial 2 (tested positive in interventional screening practices in trial 1)

Characteristics	**Standard care (number of practices = 21) (number of patients = 91)**		**Community care (number of practices = 29) (number of patients n = 129)**	
	No	**%**	**No**	**%**
Gender				
Female	38	41.8%	57	44.2%
Male	53	58.2%	72	55.8%
Missing	-	-	-	-
Ethnicity				
Black	4	4.4%	4	3.1%
Bangladeshi	4	4.4%	7	5.4%
Indian	5	5.5%	6	4.7%
Pakistani	64	70.3%	74	57.4%
Other Asian	1	1.1%	9	7.0%
Eastern Caucasian	8	8.8%	2	1.6%
Other	5	5.5%	27	20.9%
Age (years)				
mean (sd)		45.9 (12.5)		45.2 (13.5)

Table 11: Treatment follow up for patients who tested positive in the study

	Standard care (number of practices = 21)		**Community care (number of practices = 29)**		**Total**	
	Number	**%**	**Number**	**%**	**Number**	**%**
Number of patients tested positive	**n = 91**		**n = 129**		**n = 220**	
Engaged in therapy						
Denominator	**n = 91**		**n = 129**		**n = 220**	
Yes	80	87.9%	105	81.4%	185	84.1%
No	11	12.1%	24	18.6%	35	15.9%

Table 12: Engagement in clinical management plan: community care vs standard care

Type of care	Number of patients engaged in therapy		Incidence rate ratio* [95% confidence interval]	p - value
	Number	%		
Standard care *(number of practices = 21)*	80 / 91	87.9%	Ref	
Community care *(number of practices = 29)*	105 / 129	81.4%	0.759 [0.228 to 2.531]	0.654

*adjusted for site, number of eligible patients, gender and age

**Intracluster Correlation Coefficient = 0.008

Given the heterogeneity of treatment options in the ITT analysis and the varied opportunities for patients we conducted a descriptive analysis of patient disposition to identify patient outcomes. Figure 5 shows the outcomes for all patients diagnosed in intervention practices. A total of 141 patients were diagnosed in primary care with either hepatitis B or hepatitis C requiring further investigation/therapy. Of these 141 patients 131 (93%) attended for further investigation (Figure 6) and of the 96 HBsAg positive patients 83 (86.4%) engaged with care (protocol defined) (Figure 7). Of the 35 HCV positive patients 34 (97.1%) engaged with care (Figure 8).

The per protocol outcomes for the patients with hepatitis B are shown in Figure 7. In the 71 patients managed in secondary care (standard care) 61 required observation and 51 (83.6%) complied. Of the 10 requiring antiviral therapy all successfully initiated therapy and, at the time of writing 3 had achieved undetectable HBV DNA. Overall complinace was therefore 61 of 71 (86%) in standard care. Of the 25 patients treated in the community 21 of 24 (87.5%) complied with the recommended monitoring and 1 complied with therapy (overall compliance 88%).

For patients diagnosed with chronic hepatitis C all patients, regardless of treatment arm underwent disease severity assessment. All complied with clinical recommendations but given the impending availability of all oral antiviral therapy some decided to defer treatment initiation (Figure 8). Of the 27 patients undergoing treatment in secondary care 17 received treatment with an IFN based therapy, 2 received DAAs and 8 are waiting to initiate therapy. Of the 8 patients in community care 6 were treated with an IFN based regimen and 2 were treated with DAAs. Figure 10 shows the response rates and shows that 11 of 13 treated patients in secondary care achieved an SVR compared to 6 of 7 in the community. The small numbers and heterogeneity of the treatments prevent a formal comparison of the two treatment modalities but there was no evidence of improved compliance in patients treated in the community and given the excellent compliance with management in patients receiving hospital based care we found no evidence to support transfer of treatment to a community setting for this cohort of patients.

Figure 5 Patient outcomes by protocol

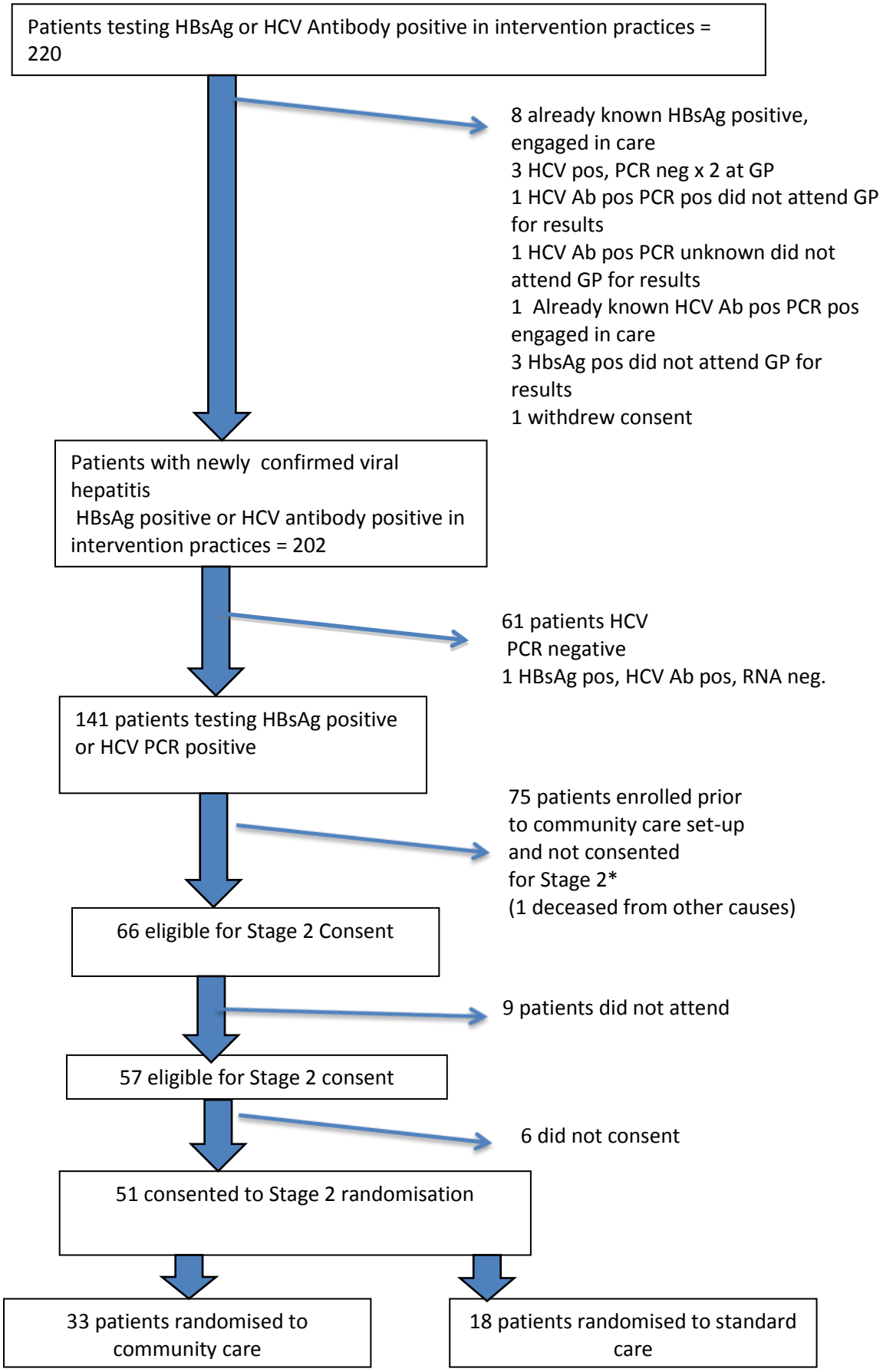


Figure 6 Engagement for the 141 diagnosed patients

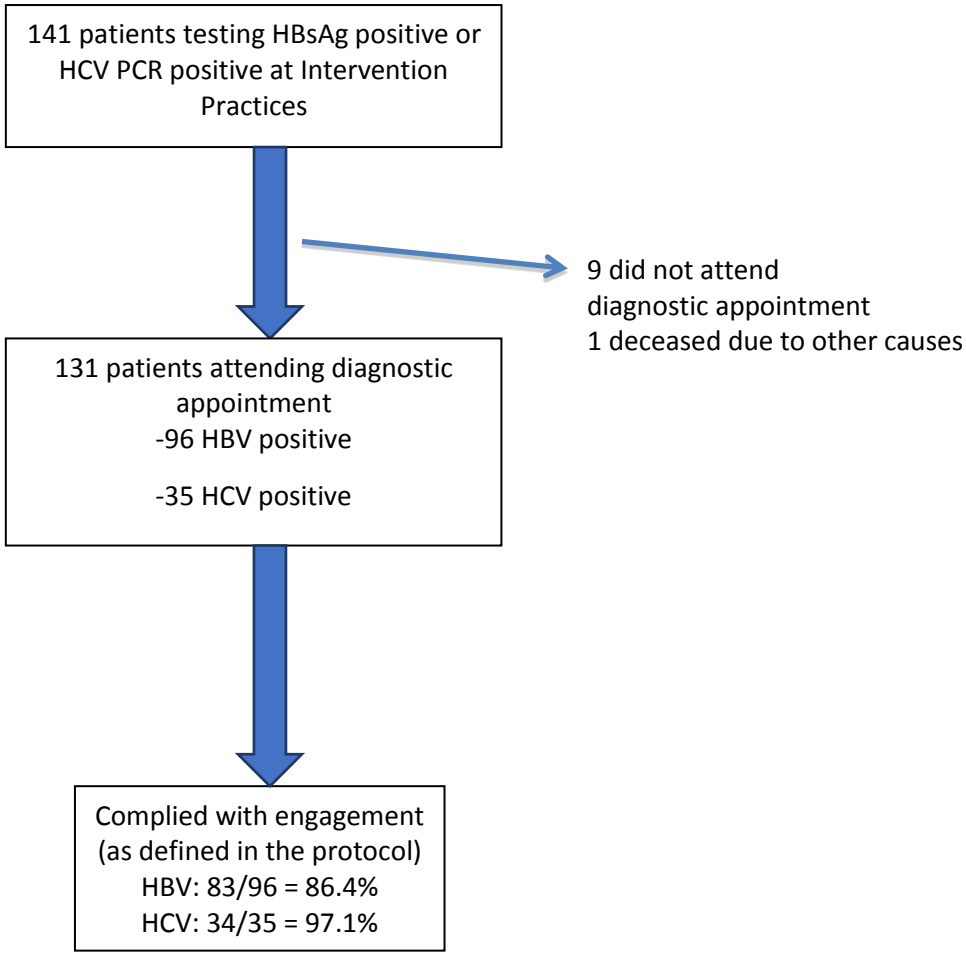


Figure 7 Outcome for HBsAg positive patients

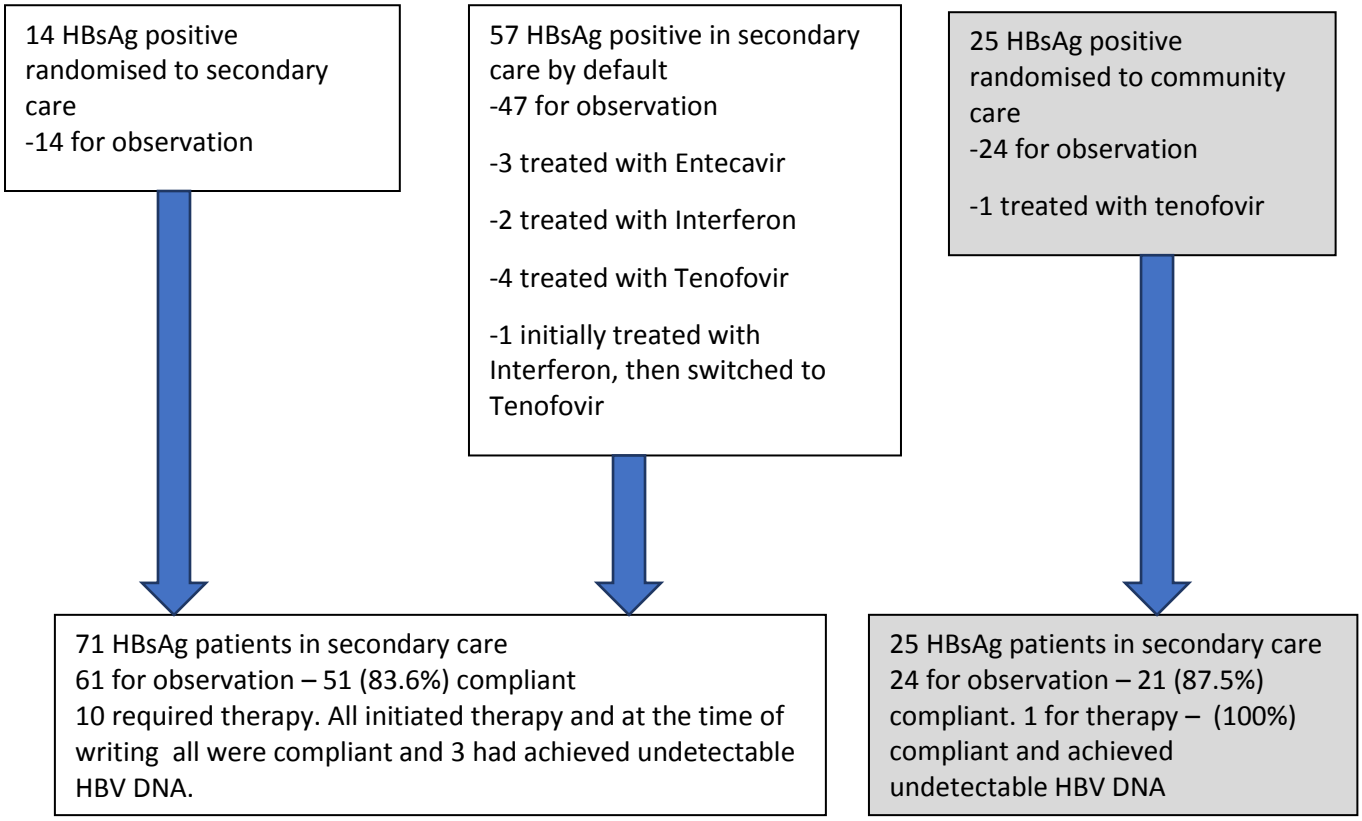
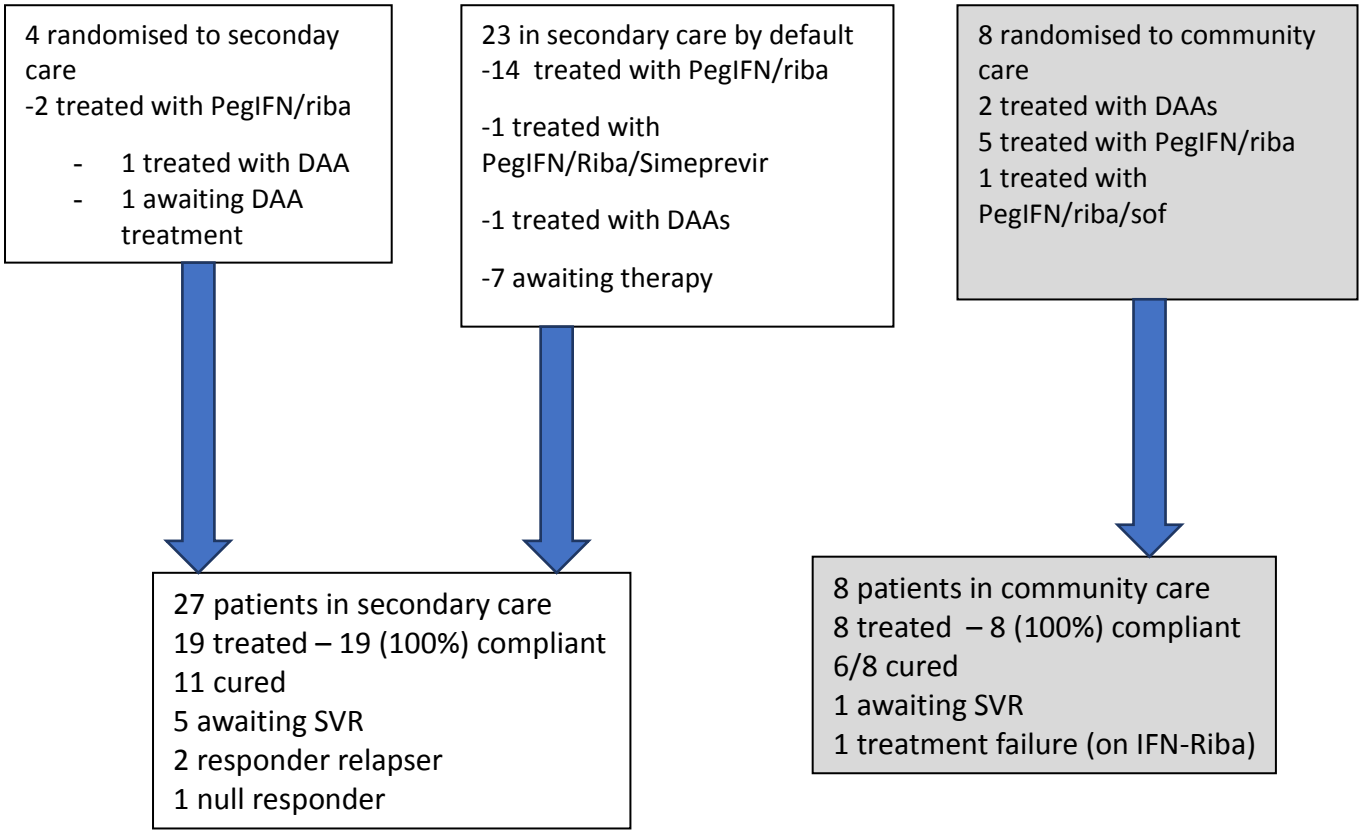


Figure 8 Outcomes for HCV Ab and RNA positive patients



11.4.1 Disease severity

97 patients were newly confirmed HBsAg positive and completed a full diagnostic assessment. Two patients (2%) had chronic hepatitis delta virus infection, 5 were HBeAg positive and the remainder were HBeAg negative. Seven patients (7%) had severe fibrosis or cirrhosis diagnosed by liver biopsy or transient elastography.

Forty five patients had HCV viraemia. Forty (88.8%) had genotype 3 and five (11.1%) had cirrhosis or advance fibrosis. There were no cases of co-infection with HBV/HCV or HIV and no cases of hepatocellular carcinoma.

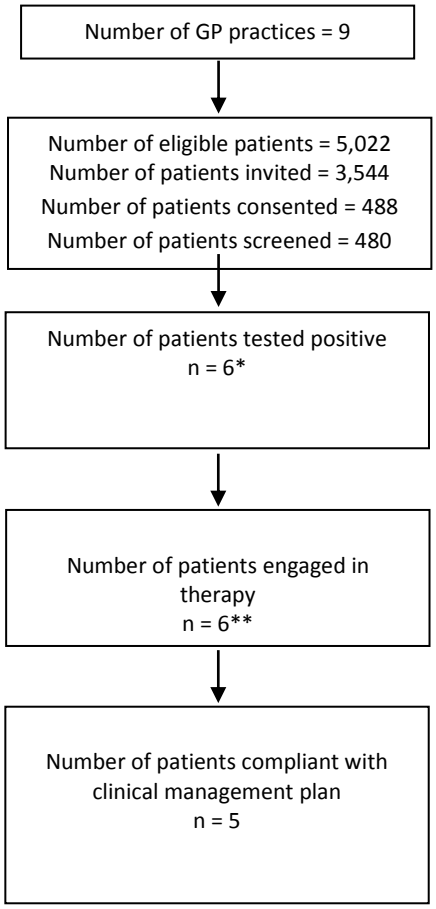
11.5 Significant adverse events

There were no significant adverse events during the study – 1 patient died from bladder cancer and 1 patient developed abnormal thyroid function tests

12. HepFREE 2 Results

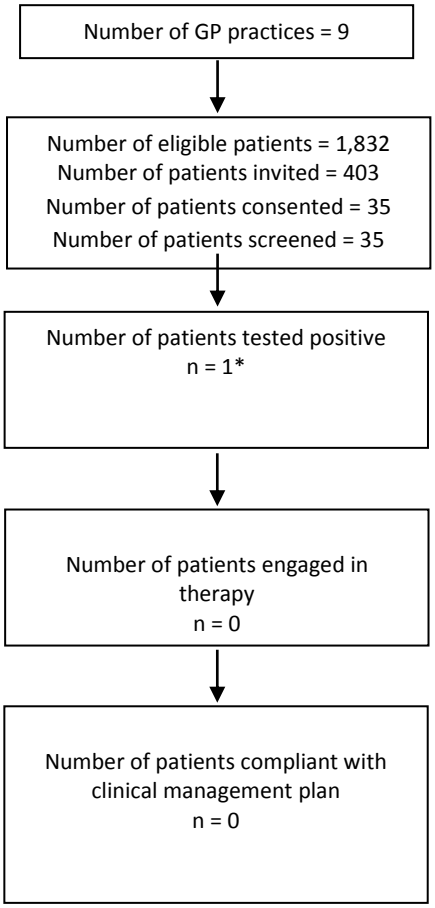
The consort flow charts for HepFREE2 are shown in Figures 9 and 6 and the demographics of the study population are shown in Table 13

Figure 9 CONSORT flowchart for HepFREE 2 study



*tested positive for Hepatitis B
**management plan is observation

Figure 10 CONSORT flowchart for HepFREE2 study (new registrants)



*tested positive for Hepatitis B

Table 13: Characteristics of patients in HepFREE 2

Characteristics	Original registrants Number of practices = 9				New registrants Number of practices = 9				All patients Number of practices = 9			
	Number of eligible patients = 5,022		Number of patients screened = 480 (9.6%)		Number of eligible patients = 1,832		Number of patients screened = 35 (1.9%)		Number of eligible patients = 6,854		Number of patients screened = 515 (7.5%)	
	No	%	No	% of total	No	%	No	% of total	No	%	No	%of total
Gender												
Female	2,777	55.3%	295	10.62%	1,009	55.10%	21	2.08%	3,786	55.20%	316	8.35%
Male	2,245	44.7%	185	8.24%	823	44.90%	14	1.70%	3,068	44.80%	199	6.49%
Missing	-	-										
Ethnicity												
Black	471	9.4%	45	9.55%	109	5.90%	3	2.75%	580	8.50%	48	8.28%
Bangladeshi	90	1.8%	10	11.11%	20	1.10%	1	5.00%	110	1.60%	11	10.00%
Indian	508	10.1%	50	9.84%	145	7.90%	4	2.76%	653	9.50%	54	8.27%
Pakistani	266	5.3%	19	7.14%	47	2.60%	1	2.13%	313	4.60%	20	6.39%
Other Asian	839	16.7%	225	26.82%	188	10.30%	11	5.85%	1,027	15.00%	105	10.22%
Eastern Caucasian	541	10.8%	37	6.84%	133	7.30%	6	4.51%	674	9.80%	43	6.38%
Other	2,307	45.9%	94	4.07%	1,190	65.00%	9	0.76%	3,497	51.00%	234	6.69%
Age (years)												
mean (sd)	39.9 (13.8)		44.9 (13.9)		35.2 (11.2)		43.7 (14.6)		38.6 (13.3)		44.8 (13.9)	

In patients registered with the practice the overall screening rate was 480 of 5,022 (9.6% (CI = 8.8-10.4%)) compared to a rate of 10,524 of 51,773 (20.3% - (CI 20.0-20.6%)) seen in intervention practices in areas of high immigrant prevalence. Screening rates in new registrants in an area of low prevalence was 35 from 1832 (1.9% (CI =1.4 – 2.6%)) compared to 862 from 6,739 (12.8% (CI = 12-13.6%)). Overall screening in an area of low immigrant density was 515 from 6854 (7.5% (CI 6.9-8.2%)) which compared to 11,386 from 58,512 (20.23% (CI =19.9-20.6%)). Hence screening in low prevalence areas is less effective.

13. Cost effectiveness

13.1 Review of previous cost effectiveness studies

There are over forty studies which examine the cost effectiveness of screen and treatment strategies for HBV and HCV. These date back to 1982 and originate from a variety of countries and cover a broad selection of higher risk groups as well as general population screening. They are comprehensively summarised within six systematic reviews dating from 2010-2016 [13-18]. There have been significant developments in both HBV and HCV drug treatment over the timescale of these studies limiting the relevance of these studies.

In general, screening for hepatitis C is reported to be highly cost-effective in a broad range of populations. According to Coward et al[17], and using a willingness to pay threshold (WTP) of £30,000 per QALY, these would include cohorts based on a range of birth year, people who inject drugs (PWID) and high risk populations, with the exception of prisoners, about whom they comment that 'surprisingly, screening programmes for prisoners appear not to offer good value for money.' Geue et al[13], on the basis of 31 studies conducted between 1999-2015, note a potential relationship between the age of the study on the one hand, and the assumed treatment effectiveness and cost. They cite prevalence of HCV in the screened population, as well as other parameters such as the progression to cirrhosis and the prevalence of difficult to treat genotypes, as potentially important parameters. Hahne et al[14] also find a broad consensus that screening of PWID is likely to be cost effective. John Baptiste et al[16] found that screening and treatment interventions for hepatitis C were generally cost effective except in specific groups such as immune compromised patients with genotype 1 infections. Sroczynski et al[15], in an earlier review dating from 2009, conclude that screening and treatment for HCV is likely to be cost-effective in higher prevalence but not lower prevalence populations. This concurs with the findings of Geue et al[13] and suggests a possible relationship between the introduction of direct acting antiviral treatments for hepatitis C, with better side effect profiles and greater effectiveness, although at a higher cost.
In terms of screening for HBV, Geue et al[13] (16 studies) conclude that this might only be effective in immigrant populations due to the tendency for higher prevalence, although they note a lack of recent evidence. Hahne et al[14] suggest that screening of PWID and pregnant women is likely to be cost effective, and further report a study suggesting that screening for HBV in the general population might be cost-effective, but express concerns about some unrealistic assumptions. In total [19], demonstrate that screening migrants for HBV might be cost-effective.

13.2 The HepFREE cost utility model

Our analysis directly compares two cohorts of patients modelled across separate screening and treatment scenarios. In the intervention arm of the model, the screening algorithm is applied according to the study protocols and subsequent treatment pathway and outcomes modelled accordingly. This is compared to the control arm, current practice, where positive cases are only found by opportunistic blood testing or following clinical intuition. Key outputs from the model include the health benefits accrued from the HepFREE screening programme. In the intervention arm of the model, a proportion of eligible patients will respond to invitation, and a further proportion will be discovered to have HBV or HCV infection. The proportion of positive cases amongst the respondents is then used to estimate the overall number of positive patients in the modelled eligible cohorts. The intervention and control screening cohorts are the same size, and each contains the same number of modelled positive cases. This is achieved by numerically scaling the control arm source data from the HepFREE study so that the total number of eligible patients is the same as in the intervention arm. We further apply the numerical scale factor both to the number of patients tested and the number of positive cases found. The modelled positive cases in each cohort then undergo a simulated life time follow up to assess the clinical implications of having viral hepatitis. As this happens, some patients not discovered during the initial intervention/control period are subsequently discovered by a combination of patient screening, and the presentation of

symptomatic patients whose condition has deteriorated sufficiently. The costs and benefits accrued over both the initial case finding period/control comparison, and the subsequent follow up are estimated and compared in order to generate measures of cost-effectiveness. Parameter values for the model were obtained from the trial data in the case of the screening algorithm replication, whilst searches of the literature were performed to estimate transitions and quality of life measures for the long term follow up. Costs not available from the trial data were obtained from published NHS a national tariff values. A number of positive cases in each arm of the model will not be identified due to the fact that only a small proportion of overall patients are ever screened, and because some of the remaining patients' disease will never progress sufficiently to produce symptoms.

13.3 Summary description of the model

Our cost-effectiveness model was developed in Microsoft Excel® using a state-transition approach, based on Markov processes, for a hypothetical population of interest. The model represents the disease process through a series of discrete health states with possible transitions between these states occurring at fixed time intervals (i.e. the cycle length). In our model the cycle length is three months. Aggregated costs and health outcomes are estimated over the total lifetime for the population by associating cost and quality of life (QoL or utility) measures to the period of time spent in each state. Our model follows two hypothetical cohorts of people: those included in the screening programme (the intervention arm) and the control group in whom spontaneous presentation for testing occurs throughout the model time span. The cost-effectiveness of the screening programme is then calculated as the difference in total cost between the two arms of the model relative to the difference in QALYs gained. A range of sensitivity and scenario analyses are included to test the relative importance of the input parameters and we have conducted probabilistic sensitivity analysis to understand the level of confidence that can be given to the outputs.

13.4 Structure of the model

The model is divided into two sections, one represents the processes in the HepFREE screening algorithm and the equivalent processes in the control arm, the other models the long term follow up for both patient groups (including the patients that are not initially detected).

In the screening algorithm, a number of GP practices are set up to perform screening, which involves GP and nurse familiarisation with procedure, along with database set up, and staff training. Following set up, eligible patients are identified by GPs and nurses, and invitations sent. A proportion of patients may be sent a reminder text or be reminded to take up screening if they attend the surgery for an interim appointment. In our model, these events are assumed to occur at outset and have no timeline since this not relevant to the economic outcome, although all personnel time and administration costs are included. For simplicity, we assume in the base case of the model that 10% of patients received reminder texts. Figures 11 and 12 below show the testing pathway for the control and intervention arm of the model.

Figure 11: Control Population testing algorithm

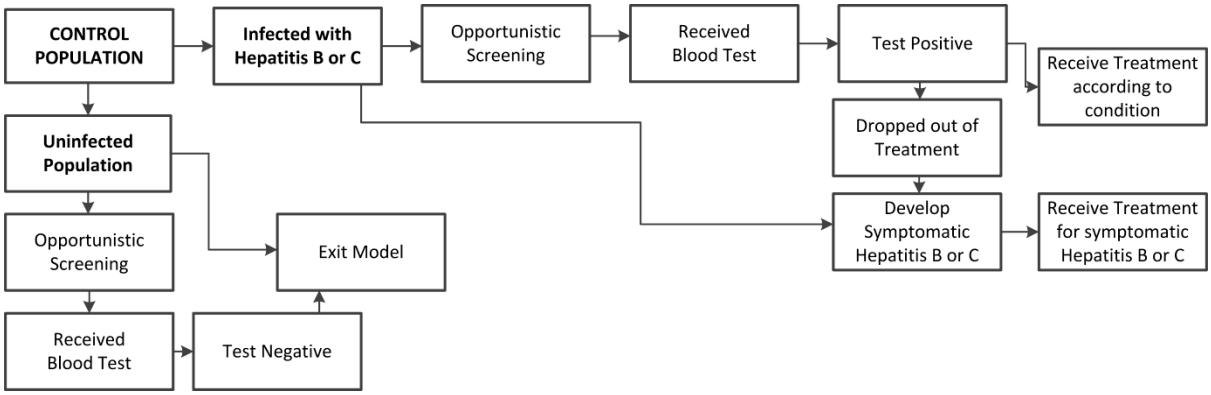
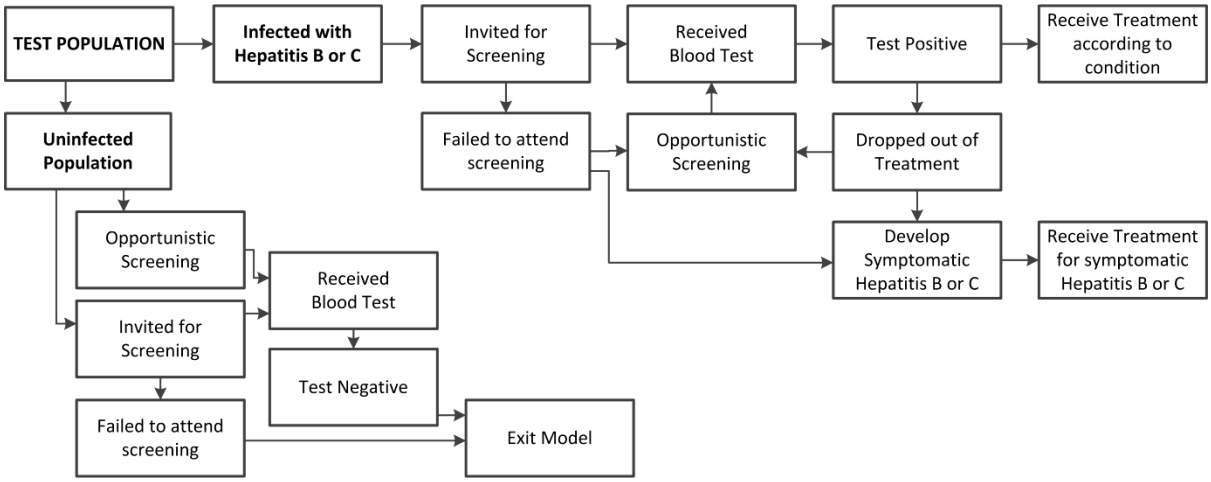


Figure 12: Intervention Population testing algorithm



Attendance and consenting, blood testing and discussion of the results with practice personnel is modelled in terms of associated cost. Some GP practices may refer patients to external phlebotomy services, which may have an impact on the number of patients who do not present for testing. Given that the number of patients who did not present for blood testing was approximately 1% overall, for simplicity we do not model this possibility in the base case. Following referral of detected positive cases to HepFREE, the follow up of these patients is modelled as three visits. These visits are modelled in terms of cost according to current NHS tariffs. In the first visit, patients who simply have cleared HCV infection are discharged, whilst a proportion of the remaining HBV and HCV positive patients undergo biopsy or other test and ultrasound in order to stage their disease. In the third visit, patients are assigned to treatment options according to current listed treatment prices. Drug injections that can be carried out by patients at home after some initial training are modelled as the cost of the drug plus an estimate of the amount of nurse time required to train in self-injection. Following simulated treatment, patients are allocated to the long term follow up section. In the control arm, a proportion of patients (as represented by the model data) are costed as seeing a GP and being invited to have a blood test. Any positive results are referred to hospital and are assumed to be managed in a similar way to the HepFREE algorithm for ease of comparison.

Figures 13 and 14 below show the modelled progression pathways for patients infected with HBV and HCV respectively.

Figure 13: Progression Pathway for HBV infected patients

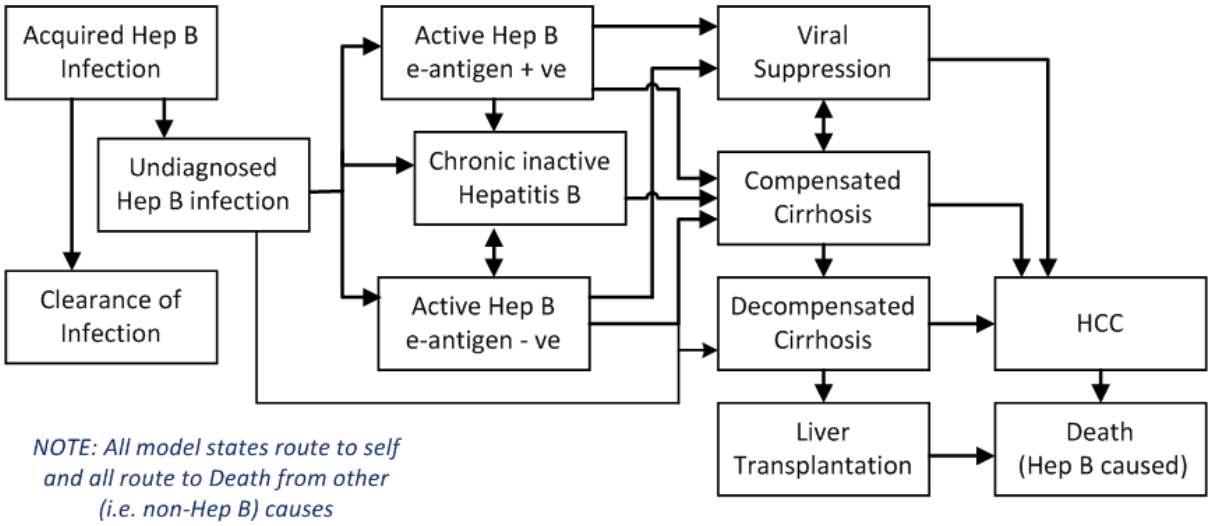
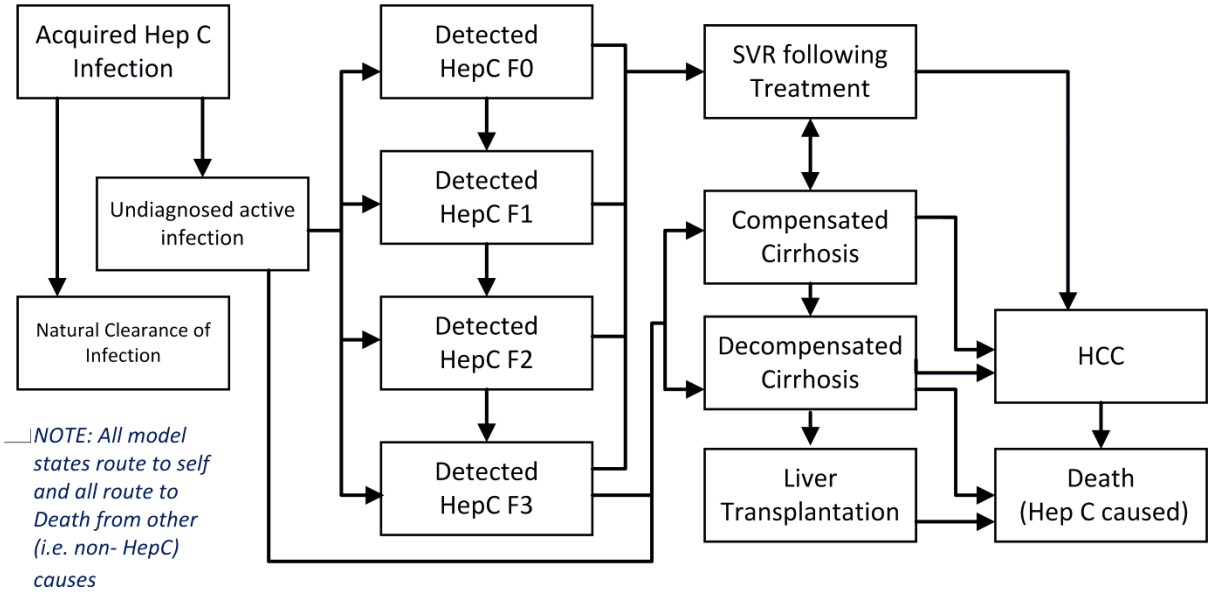


Figure 14: Progression Pathway for HCV infected patients



13.5 Description of Disease States

In the long term follow up section of the model, the same structure and transition probabilities are applied to both arms. Differences between the arms are therefore driven by the different population levels in each state resulting from inclusion into the screening programme. The long-term follow up section hence measures the difference in health benefits and costs between the two arms of the model, based on the fact that, of a known number of positive cases, different numbers will be detected by the initial testing. Patients who are detected and treated in either arm of the model are therefore assigned to an appropriate state of the Markov model. This is typically chronic inactive disease or viral suppression in the case of hepatitis B patients, or SVR in the case of hepatitis C patients. Simulated patients who were not detected by the initial procedures are assigned to a state of undiagnosed but chronically infected. It is assumed that during long term follow up, a level of screening activity continues in both arms, according to that initially estimated in the control arm, and in addition, that some patients will present with symptoms according to the

natural history of the disease. A number of patients in each arm may not present at all, since the proportion of patients detected annually by screening is low, and some patients' disease never progresses sufficiently to develop symptoms. Patients who present or are detected during the long term follow undergo similar diagnostic and staging procedures to those in the initial processes. For simplicity, these are assumed to take place during one model cycle. HCV patients with undetectable viral RNA, assumed to be no longer infected, are seen for a single visit and discharged, reflecting the new recommendations that the first sample undergoes reflex HCV RNA testing. We elected to omit the possible need for a second, confirmatory test as clinical opinion is divided on its value and in large scale screening it is likely to be omitted. Other HBV and HCV positive patients receive treatment according to similar protocols as the screening algorithm. HBV patients are treated with interferon first line or entecavir /tenofovir if they do not achieve viral suppression in line with UK NICE guidelines. Other treatment algorithms do exist but the cost differential is minimal and for simplicity we chose to follow the UK NICE model. Patients are then followed up for life. HBV patients continue to take viral suppression as appropriate. Patients whose disease progresses, with or without treatment, may develop cirrhosis. If the cirrhosis decompensates they may be placed on a transplant waiting list, or die of complications of liver disease. A further proportion of patients may die whilst waiting for a transplant. The remainder of these patients will have surgery and post-surgical follow up (costed to include hospital visits, immune suppression, and treatment of periods of ill health according to Singh 2014). A proportion of simulated transplanted patients may develop liver failure due to viral reinfection of their transplant. We model a single repeat transplant per patient, in this case, such that in the case of further failure the patients will die of liver cirrhosis. It is assumed that patients over 70 years of age would be very unlikely to be considered for transplantation.

Patients with liver cirrhosis may develop HCC. Given that development of HCC without cirrhosis is rare [20], we assume for simplicity that this does not occur in the base case of our model, and that therefore patients with naturally cleared infection do not develop HCC. Treated patients with cleared HCV infection or suppressed HBV infection may develop HCC according to the proportion assumed to have developed cirrhosis before treatment. In the same way, patients with undetected disease may spontaneously present with HCC according the same rationale. Patients who develop HCC receive palliative treatment only in the base case.

13.6 Probabilistic sensitivity analysis

Parameter values used for modelling carry with them uncertainty, because the parameterisations typically represent estimates of an average. Sensitivity analysis allows us to assess the potential impact of parameter inaccuracies on the results of the model, thereby indicating how 'sensitive' the model results are to each potential inaccuracy. We varied the value of every parameter in the model in turn, using ranges of plausible values for each one (appendix A), and then applied a probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. This technique draws every parameter value randomly from a statistical distribution. We generated 5,000 such combinations of parameter values using standard probability distributions. We used these results to infer the probability of screening being cost-effective when compared to a willingness-to-pay (WTP) range of £20,000 to £30,000 per QALY gained. This is the range used by NICE in assessing what constitutes a cost effective use of resources in the UK NHS[21].

13.7 Sources of estimates for HepFree model

13.7.1 Structural parameters

Screening algorithm: The timeframe of the screening algorithm is essentially the time taken to invite, screen, test, stage and treat a positive case. For simplicity therefore, it assumed that the positive cases are all detected simultaneously. No quantifiable healthcare benefits accrue during the screening algorithm, the variables are simply the costs of case finding and management.

Progression Model : The Markov model represents the patient pathway subsequent to testing, diagnosis and treatment and has a lifetime horizon owing to the fact that the additional quality of life benefits of treating, and potentially, curing viral hepatitis earlier are lifelong, and also include preventable deaths from liver failure, liver transplantation complications and hepatocellular carcinoma. The cycle length used in our model is 13 weeks (4 cycles per year), this was chosen to represent a typical timeframe for many of the antiviral treatments employed and is consistent with other cost effectiveness studies in this area[22]. Both costs and benefits in the model are discounted at 3.5% per annum in accordance with the standard guidelines of the National Institute for Health and Care Excellence (NICE)[21]. Discounting rates in other countries that have produced comparable studies are 4%/1.5% (Netherlands)[19] and 5%/5% (Canada)[23]. The impact of health benefit discounting is likely to be particularly important since many of the health benefits of the intervention will occur several years after early intervention and treatment.

13.8 Costs

The cost estimates used in the model can be divided into a series of categories which are shown in Tables 1 and 2 below

13.8.1 Screening Cost Estimates used in the model

Table 14 :Annual costs associated with Markov Model states

Model STATE	Annual cost	Source
HEPATITIS B STATES		
Presentation and treatment	£941	Based on 1x component A, B and C
Viral suppression	£498	Based on 2x components B and C
Chronic Inactive Hep B (CHB)	£498	Based on annual follow up at tariff A or B
Active Hep B e-antigen positive	£498	Based on 2x components B and C
Active Hep B e-antigen negative	£498	Based on 2x components B and C
Compensated cirrhosis	£996	Based on 4x components B and C
HEPATITIS C STATES		
F0	£498	Based on 2x components B and C
F1	£498	Based on 2x components B and C
F2	£498	Based on 2x components B and C
F3	£498	Based on 2x components B and C
SVR	£498	Based on 2x components B and C
Compensated cirrhosis	£996	Based on 4x components B and C
BOTH HEPATITIS B AND C		
Seroclearance	£361	(One appointment only)
Decompensated cirrhosis	£13,858	NICE guideline NG 50 "Cirrhosis over 16s, assessment and management." July 2016 appendix N. Source data is reported as the cost per 6 months
Transplantation Waiting list	£18,055	Singh and Longworth 2014[24]
Transplant surgery	£64,452	Singh and Longworth 2014
Post-transplant and healthy Years 1 & 2	£36,009	Singh and Longworth 2014
Post-transplant & healthy Yr 3 onwards Hepatitis B Hepatitis C	 £14900.00 £1880.00	"Cirrhosis over 16s, assessment and management." July 2016 appendix N. Source data is given as the cost per 6 months
Hepatocellular carcinoma	£13,858	NICE guideline NG 50 "Cirrhosis over 16s, assessment and management." July 2016 appendix N. Source data is given as the cost per 6 months

COMPONENT COSTS		
A: Initial consultation	£361	Multi professional first appointment consultant led NHS national Tariff WF02B 2017-18
B: Follow up appointments	£204	Follow up appointment, multi professional NHS national Tariff WF02A 2017-18
C: Annual surveillance for HCC	£45	RD40Z. Ultrasound scan lasting less than 20 minutes without contrast
D: Liver Biopsy	£535	BO4Z Endoscopic /radiology category 1

13.9 Treatment cost estimates

13.9.1 Drug Costs

Drug treatment costs are sourced from British National Formulary (latest available edition). Costs of interferon treatment include some costs of initial nurse administration after which patients may self-inject. For this report we used the treatments used during this trial but in this rapidly changing environment we are aware that treatments have evolved. To incorporate these changes we modelled changes in drug costs to allow for new treatment strategies at reduced cost (see later). The cost of pegylated interferon and ribavirin includes the cost of genotype 3 patients who may fail treatment and need to be retreated with sofosbuvir based regimens.

Table 15:Values for cost of drugs used in economic model

Drug	Cost per week	Cost per course of treatment	Source
Hepatitis B drugs			
Interferon	£497.76 (plus cost of nurse administration and training to inject)	£1646.72	BNF 69/ NICE guideline NG 50 "Cirrhosis over 16s, assessment and management." July 2016 appendix N. Source data as 6 monthly costs.
Tenofovir	£47.75	£620.75	
Entecavir	£84.75	£1101.75	
Hepatitis C drugs			
Pegylated Interferon/ribavirin	£189.85	£14259.64 (includes cost of G3 treatment fails that subsequently receive DAAs)	BNF 69/ NICE guideline NG 50 "Cirrhosis over 16s, assessment and management." July 2016 appendix N. Source data as 6 monthly costs.
Sofosbuvir	£2915.25	£34983	
Sofosbuvir/Ledipasvir (HARVONI)	£3248.33	£25986.66 (8 weeks)	
Sofosbuvir/Velapatasvir (treatment of cirrhosis in G3 failed PegRiba)	£3248.33	£38980 (12 weeks)	
Simeprevir	£2458.10		
Grazeprevir/Elbasvir (genotype 4)	£3041.75	£36501 (12 weeks)	

13.9.2 Utility Estimates

We apply utility weights to simulated patient populations in the model, such that the number of model cycles spent by simulated patients in each health state is weighted by an estimate of the quality of life associated with that state. Consequently, as the model runs, the aggregation of

the weighted time spent across the health state becomes the overall number of Quality Adjusted Life Years (QALYs) experienced by each cohort.

Recent studies have used a number of sources of data to inform quality of life measurements. NICE has a preference for utility measures based on generic elicitation protocols, typically the EQ5 [21]. EQ5D based measures of utility have been published by Wright and Grieve [25], and by Chong et al [26] for hepatitis C disease states. We use the data of Wright and Grieve since these have been used for a number of health technology appraisals in connection with hepatitis C, including recent appraisals of direct acting antiviral treatments.

A number of datasets exist for hepatitis B disease states. Some use EQ5D elicitation but have some interesting features. Clearly where there are health states common to both HBV and HCV one would expect to find values that are broadly similar if not identical. However, for example, Lee et al[27], in a study of 4019 Korean patients, found values of 0.80, 0.67 and 0.77 for compensated cirrhosis, decompensated cirrhosis and HCC respectively, compared to 0.55 and 0.45 in the Wright data. These values, especially for decompensated cirrhosis and HCC seem to be rather high, given that the conditions have a five year survival typically less than 20%[28]. This is not particular to the EQ5D, since Woo et al[29], in a study of patients from Toronto General Hospital clinics in which participants were required to be fluent in either English, Mandarin or Cantonese, found values for decompensated cirrhosis and HCC, of 0.73 and 0.81. These values suggest a quality of life comparable with being a healthy individual aged between 65-80. Also, in both cases, given that HCC is very rare in patients without cirrhosis[20], it is curious that HCC is associated with (significantly) higher utility. Further exploration of these issues is beyond the scope of this report. The elicitation method may be partly responsible, since values for decompensated cirrhosis of 0.49 and 0.82 have been elicited using the Canadian Health Utilities Index version 3(HUI3) and standard gamble respectively. We note that Wong et al[23,30] found potential variability between $CDN50, 000 to $CDN100, 000 per QALY (base case $CDN 69,209) in their utility value data.

A set of values obtained by Levy et al[31] using standard gamble and visual analogue scale elicitation, has been used in previous studies of HBV, notably Veldhuijzen et al, Toy et al, and in recent NICE appraisals. These might be considered to show similar orders of magnitude to our values for HCV (e.g. decompensated cirrhosis = 0.38 (Levy et al) vs 0.45(Wright and Grieve)). Our considered decision therefore, was to use these values. We follow Toy[32] in distinguishing between chronic and active hepatitis B, and again, note the alternative 0.68 value for pre-cirrhotic disease (Veldhuizen 2011, Toy 2012) as being somewhat out of keeping with a value of 0.69 for compensated cirrhosis. This was probably a typographical error, since Eckmann et al use a value of 0.86 based on the same data[33]. Since no standard errors are quoted in the source data, we inferred for our probabilistic sensitivity analysis a standard error of 0.01, from the fact that Veldhuijzen et al used a range of approximately +/- 0.02, and assuming a normal distribution.

All disease state utility values used in the model were age adjusted to reflect that fact that the quality of life of a healthy population declines over time. The mean utility of a healthy population was calculated for each year of age of the cohort over time. For each individual health state value, the mean age of the population from which the value was derived, was mapped to the utility value that a healthy population of that age would have, according to the data of Ara and Brazier[34]. The resulting multiplier was applied across the age range of the study to produce an age specific disease state value.

We made two further adjustments. First, we did not allow that mild disease states such as chronic inactive hepatitis B could have a higher utility than a healthy population of the same age. Second, in the probabilistic sensitivity analysis (PSA), we aimed to control the possible scenario whereby a state implying worsening of disease could have a higher randomly generated utility value than a state implying less severe disease. Since the correlations between mean utility values for each state were not known, this was achieved simply by not allowing a value for a worsening state to exceed that of a less severe state.

Table 16 below shows the values used for utilities in each of the states of our model for both HBV and HCV.

Table 16 State utilities used in economic model

Utility Parameter	***Value***	***SE***	***Source***
Hepatitis B			
Undetected Hepatitis B[1]	0.95	0.01	Levy et al
Seroclearance[1]	0.95	0.01	
Viral suppression[1]	0.95	0.01	
Chronic inactive disease[1]	0.95	0.01	
Active disease, e positive	0.85	0.01	
Active disease, e negative	0.85	0.01	
Compensated cirrhosis	0.69	0.01	
Decompensated cirrhosis	0.35	0.01	
Post-transplant surgery	0.67	0.01	
HCC	0.38	0.01	
Utility Parameter	***Value***	***SE***	***Source***
Hepatitis C			
Seroclearance/SVR	0.82	0.0005	Castelnuovo et al
Undetected	0.79	0.024	
F0	0.75	0.024	
F1	0.75	0.024	
F2	0.75	0.024	
F3	0.75	0.024	
Compensated cirrhosis	0.55	0.054	
Decompensated cirrhosis/HCC	0.45	0.056	

13.10 Transition Probabilities

Transition probabilities and associated parameters used in the long-term follow up of the model are derived from recently published economic models (table 17). Transitions for patients with hepatitis B infection are based upon data from Veldhuijzen et al[32]), whereas transitions for patients with hepatitis C infection are derived from the metaregression of Thein et al[35], based upon the number of reviewed studies in which disease progression was estimated from patients attending hepatology clinics.

Untreated patients who enter the model, do so with a probability calculated from an estimate of the numbers of patients detected annually by the control arm of the study, and adjusted for the length of the model cycle. We further assume that patients whose disease has naturally progressed to decompensated cirrhosis will present with symptoms and signs of impending liver failure. Our approach leads to a spontaneous presentation for both patients with HBV and HCV, of ~5% per year for the base age of our model (age 38). Patients with treatable hepatitis B infection receive treatment over 4 model cycles to reflect the 48 week timespan of treatment. Patients with hepatitis C infection are assumed to complete treatment over the course of a single model cycle. By comparison, in a previous study, Castelnuovo et al [22] varied the rate of spontaneous presentation from 3.8% to 7.7% annually, based on data collected in Scotland between 2000 and 2005. For patients infected with HBV we assume a 95% probability of viral suppression in the base case, and a 90% probability of achieving SVR for patients infected with HCV.

Additional data from annual NHS UK liver transplantation audit were used to inform transplant survival and the probability of retransplant in the case of transplant failure. Patients transplanted because of documented HBV or HCV infection have an estimated five year transplant survival of 80.3% (95% CI 73-85.2%, data from 2006-2010). We assume that an exponential model of survival is an adequate fit for the survival of transplants, based on the fact that a calculated one year survival, based on this assumption is 95.9%, compared to the measured 95.4% (data from 2010-14). Patients with inactive or slowly progressing disease may die of causes unrelated to their liver disease. For this, we use age adjusted probabilities derived from UK Government actuary tables.

Progression from HCV achieved SVR to HCC has been measured in Japanese patients with HCV. Over seven studies, 47/2482 (1.9%) of patients developed HCC over a follow up of 40 months or more, suggesting an annual probability of 0.5% of developing HCC[20]. It is known however, that Japanese patients are more susceptible to developing HCC. Unusually, some of these patients had precirrhotic degrees of liver fibrosis. Other estimates suggest that the risk of developing HCC is attenuated by 75% in patients with SVR compared to patients with ongoing infection.

In the base case of the model, we assume that the risk of progression to HCC from virally suppressed patients is similar to the risk of developing HCC in patients with chronically inactive disease.

Table 17: Values of between states Transition Probabilities used in economic model

Hepatitis C transitions					
From	**To**	**Base Value**	**Low**	**High**	**Source**
F0	F1				Thein et al
Study setting:	Liver clinic	0.116	0.098	0.123	Thein et al
	Age >=40 years	0.110	0.102	0.129	Thein et al
	Studies published since year 2000	0.115	0.062	0.246	Thein et al
	Community studies	0.124	0.103	0.131	Thein et al
F1	F2				Thein et al
Study setting	Liver clinic	0.082	0.071	0.094	Thein et al
	Age >=40 years	0.079	0.069	0.090	Thein et al
	Studies published since year 2000	0.083	0.073	0.094	Thein et al
	Community studies	0.073	0.048	0.110	Thein et al
F2	F3				Thein et al
Study setting	Liver clinic	0.119	0.106	0.133	Thein et al
	Age >=40 years	0.116	0.104	0.129	Thein et al
	Studies published since year 2000	0.115	0.104	0.127	Thein et al
	Community studies	0.123	0.082	0.185	Thein et al
F3	Compensated cirrhosis F4				Thein et al
Study setting	Liver clinic	0.117	0.104	0.132	Thein et al
	Age >=40 years	0.113	0.100	0.128	Thein et al
	Studies published since year 2000	0.112	0.100	0.125	Thein et al
	Community studies	0.165	0.126	0.217	
Compensated cirrhosis F4	Decompensated cirrhosis(Dc)	0.0390	0.0300	0.0480	Coffin et al 2012
DC	Transplant waiting list	0.0310	0.0248	0.0372	Coffin et al 2012
Waiting list	Transplantation	0.71			NHS England Annual report on Liver Transplantation 2016
F4	HCC	0.0190	0.0170	0.0550	Coffin et al 2012
DC	HCC	0.0140	0.0060	0.0200	Coffin et al 2012
F4 SVR	Relapse	****			Coffin et al 2012
DC	DEATH	0.1290	0.1032	0.1548	Coffin et al 2012
HCC	DEATH	0.4270	0..3416–	0.5124	Coffin et al 2012
Transplantation	DEATH year 1	0.1			NHS England Annual report on Liver Transplantation 2016
Transplantation	DEATH yr 2 onward	0.1			NHS England Annual report on Liver

13.11 Cost Effectiveness Results

We find that a one off screening programme amongst migrant populations in the UK, for detection and treatment of both HBV and HCV, compared to usual practice, is cost effective at willingness to pay thresholds in excess of **£8,540** per QALY (see table 18 below). This is based on the whole cohort results from the HepFree trial data. The costs per case found were for £3,216 for HBV and £3,523 for HCV. The incremental cost of the programme was £1,060,339 and the total cost of the screening programme, based on the numbers tested and positive cases found, was £1,379,564 The initial set up costs were £44,505 (3% of overall cost), whilst the cost of treatment for detected HCV cases was £772,514 (56%).The overall cost of HBV treatment was £44,811(3%) based on 11 viraemic patients being treated.

Treatment of HBV cases resulted in 8.65 lifetime incremental QALYs per patient, compared to 0.81 lifetime incremental QALYs per patient treated for HCV. Screening and treatment of HBV prevented 3.69 deaths from HCC and 10.15 overall, whereas screening and treatment of HCV prevented 2.64 deaths from HCC, and 3.34 overall. There were an estimated 11.53 liver transplants across the entire simulated cohorts. Cases of HCC accounted for 276.85/386.41 (72) % of overall deaths.

Table 18: Base case outputs.

	Combined	Hepatitis B		Hepatitis C	
ITEM		Intervention	Control	Intervention	Control
Cohort No.	58512	58512	58512	58512	58512
No. Invited. Control figure reported is scaling up to same relative size as intervention cohort.		47529	1001.07	47529	1001.07
No. Tested		10524	1001.07	10524	1001.07
% Turn out level		22%	100%	22%	100%
No positive cases found (prevalence %)		115(1.093)	16.383(1.6)	105(0.998)	14.958(1.494)
Prevalence within tested cases %		1.093%	1.637%	0.998%	1.494%
Presumed overall number of positive cases in total cohort		639.54	639.54	583.95	583.95
Incremental patients identified	188.67	98.62	*	90.05	*
Number of first liver transplants.	12.18	4.84	5.62	0.88	0.85
Number of repeat transplants.	0.63	0.25	0.29	0.04	0.04
Deaths HCC	276.85	75.30	78.99	59.96	62.60
All HBV/HCV related deaths	386.41	116.79	126.94	69.67	73.01
Patients unpresented by age 66, all arms (%)	451.27	168.12(26.29)	196.67(30.76)	39.52(6.77)	47(8.05)
Natural clearance (detected)	73.12	0.00	0.00	64.00	9.12

Natural clearance (overall)	627.45	Range: 44.33-99.74			286.6
Overall incremental cost	£1,060,335	*	*	*	*
Cost of screening programme	£1,379,564	*	*	*	*
Cost of control case finding	£207,992	*	*	*	*
Practice set up costs: intervention arm	£44,505	*	*	*	*
Recruitment costs: intervention arm	£124,139	*	*	*	*
Recruitment costs: control arm	£23,356	*	*	*	*
Blood testing costs intervention arm	£201,240	*	*	*	*
Blood testing costs control arm	£20,266	*	*	*	*
HepFREE Visit 1 costs (+equivalent for control arm)	£83,628	£37,183	£5,306	£35,739	£5,399
HepFREE Visit 2 costs	£71,819	£40,732	£6,236	£21,947	£2,902
HepFREE Visit 3 costs: staff	£38,645	£7,942	£1,216	£25,270	£4,217
Visit 3 costs: treatment	£953,104	£44,811	£6,861	£772,514	£128,918
Net cost of treatment		£37,950	*	£643,595	*
Cost per positive case found		£3,216	£2,663	£3,523	£2,916
Cost per treatable case found		£37,006	£29,051	£11,589	£8,393
Cost per case found and treated (assuming whole set up cost)		£45,505	£37,550	£35,010	£31,684
Overall incremental QALYs	124.16				
Incremental QALYs per person screened		0.0090		0.0028	
Incremental QALYs per treatable case		8.6513		0.8054	
Total QALYs		10413.31	10318.15	8857.53	8828.54
AT WTP £20,000 per Q					

Net monetary benefit	£1,422,838				
Net health benefit (QALYs)	71.14				
AT WTP £30,000 per Q					
Net monetary benefit	£2,664,423				
Net health benefit (QALYs)	88.81				
ICER	**£8,540**				

13.11.1 One way sensitivity analyses

Our one way sensitivity analyses highlight what we feel to be the chief causes of parameter uncertainty and also facilitate comparison with other recent international publications on this subject (table 20). By applying Dutch national guidelines for discounting to our data, we show that this would achieve an incremental 14.0 QALYs per treated patients compared to Veldhuijzen's previously reported 13.8. Alternatively, we find that a 5% standard for utility discounting would result in 22.5 incremental QALYs for screening and treatment of HCV. By comparison, Wong et al, based on screening a general population of 25-64 year olds, and based on 37 treated patients per 10,000 patients screened, similar to our cohort, report between 32-95 incremental QALYs by the same standard. The same study reported that 9 HCV related deaths were prevented. Also using this discounting standard, we find that 69.2 incremental QALYs (6.3 per treated patient) are due to screening and treatment of HBV.

Selective screening of immigrants of Pakistani ethnicity, the ethnic group with the majority of positive cases, was found to be incrementally cost effective at WTP thresholds in excess of £9,523 per QALY. This group was the only one that had a higher proportion of cases of HCV rather than HBV. Screening of over 40s was incrementally cost effective at WTP thresholds in excess of £15,696 A threshold analysis of both the over 40s and the main cohort data suggests that the intervention would cease to be cost effective at WTP £30,000 per QALY for a cohort mean age of 57 or higher. In view of changing patterns in the treatment of HCV, we found that treating all patients with DAA regiments would be cost-effective at WTP thresholds in excess of £18,185. This reduces to £8,587 in the case of discounts of G1 treatment to £4800 per course or G3 to £10,000 per course. Treatment with sofosbuvir/lepdipasvir for treatment naive patients is assumed. This further reduces to £7,868 if over 90% of patients can achieve SVR with 12 weeks treatment or less.

At the present time, treatment of patients with HCV is much less reliant on the use of interferon ribavirin, and is largely based around DAA combinations such as sofosbuvir/velapatasvir or glecaprevir/prebentasvir. In the former case, sensitivity analysis of 12 weeks treatment with sofosbuvir/velapatasvir shows that the ICER for this combination at full list price of the drugs (£38980 for 12 weeks) is £15,908 reducing to £9,395 if the drugs are discounted to 25% of list price. A small further reduction in the ICER occurs if salvage treatment for initial treatment fails is also available at a similar discount (table 19). Full price treatment using glecaprevir/prebentasvir combinations is cost effective at WTP thresholds above £10,547 for 8 weeks of treatment (£25,987) in all cases or £16,701 for 16 weeks of treatment (table 19), assuming the use of sofosbuvir/velapatasvir (an already approved combination) for the treatment of patients with cirrhosis. This reduces to £9,316 if the glecaprevir/prebentasvir treatment combination can be obtained at a 75% discount and also would be licenced for the treatment of all patients. The above sensitivity analyses assume that 90% of patients achieve SVR with one treatment. If 98% of patients achieve SVR in the long term, as suggested by Puoti et al [36], then the ICER further reduces to £9,153 based on a 75% price discount for all patients. Table 19 below shows the effect on the ICER for different combinations of treatment alternatives.

Table 19: Cost sensitivity analysis of commonly used DAA treatment combinations

Drug combination	Duration of treatment	ICER
Sofosbuvir/velapatasvir at list price	12 weeks	£15,908
Sofosbuvir/velapatasvir at 50% of list price	12 weeks	£10,412
Sofosbuvir/velapatasvir at 25% of list price	12 weeks	£9,395
Sofosbuvir/velapatasvir at 25% of list price and salvage treatment (currently sofosbuvir ledipdasvir) at same discount	12 weeks	£9,390
Glecaprevir/Prebentasvir Sofosbuvir/velapatasvir used to treat patients in cirrhosis	16 weeks	£16,702
Glecaprevir/Prebentasvir Sofosbuvir/velapatasvir used to treat patients in cirrhosis	8 weeks	£10,547
Glecaprevir/Prebentasvir To treat all patients	8 weeks	£10,970
Glecaprevir/Prebentasvir At 50% of list price to treat all patients	8 weeks	£9,867
Glecaprevir/Prebentasvir At 25% of list price to treat all patients	8 weeks	£9,316
Glecaprevir/Prebentasvir At 25% of list price to treat all patients and assuming 98% of patients achieve SVR (default 90%)	8 weeks	£9,153
Glecaprevir/Prebentasvir At 50 % of list price. Sofosbuvir/velapatasvir at full price used to treat patients in cirrhosis.	8 weeks	£7,962
Glecaprevir/Prebentasvir At 25% of list price. Sofosbuvir/velapatasvir at full price used to treat patients in cirrhosis.	8 weeks	£6,935
Glecaprevir/Prebentasvir At 50 % of list price. Sofosbuvir/velapatasvir used to treat patients in cirrhosis at same discount.	8 weeks	£9,391
Glecaprevir/Prebentasvir At 25 % of list price. Sofosbuvir/velapatasvir used to treat patients in cirrhosis at same discount.	8 weeks	£9,078

The parameters with the greatest scope to produce variation in the result, were therefore, from our analysis, the mean age of the cohort being screened, variability in the disease progression of HBV (as also found by Veldhuijzen et al), the disease prevalence and response to invitation, potential variability in the cost of running a screening programme including the initial blood tests, and the cost of antiviral drugs for HCV. By contrast, variation in medical management costs, such as those for liver transplantation and decompensated cirrhosis, the choice of treatment for long term HBV suppression, or variations in other model parameters such as the utility of HBV disease states did not produce variation in the ICER that would amount to decision influencing. Varying the young adult distribution of disease (HCV In particular) as a proxy for age at infection, had no substantial influence on the results. A simulated doubling of HCV viraemic numbers resulted in an increase in the ICER from £8,540 to £9,764.

Table 20: Table of one way sensitivity analysis outputs

ANALYSIS CATEGORY	Rationale	Incremental cost	Inc. QALY	Inc. QALY due to HBV programme	ICER
ETHNICITY SUBGROUP ANALYSES					
Pakistani Ethnicity	This ethnic group demonstrated the greatest overall response rate to invitation and had the highest proportion of positive cases.	£754,704	79.25	52.17	**£9,523**
AGE BASED SUBGROUP ANALYSES					
Patients aged 40 and over	Statistical analysis showed marked increase in attendance and case finding in this age group.	£897,490	57.18	39.36	**£15,696**
SENSITIVITY ANALYSES OF SCREENING INVITE AND TREATMENT PROTOCOL					
Hospital vs Community treatment	This comparison was nested within the main HepFREE trial. The data used compares the number of positive patients found and treated during each arm according to treatment actually received (per protocol). The assumption is made that the visit costs are the same and no estimation has been made of the set up costs of the community program.	£635,850	60.46		**£10,518**
SENSITIVITY ANALYSES OF DISEASE PREVALENCE		These act as a threshold analysis for the cost-effectiveness of screening at lower prevalence of disease			
Prevalence of HBV and HCV 50% of baseline	In particular Eckmann, and (insert name) find that screening for HBV can be cost-effective at western populations of prevalence. These studies have received some criticism on methodological grounds	£697,502	61.64	47.61	**£11,316**
Prevalence of HBV and HCV 25% of baseline		£502,658	30.83	23.81	**£16,306**
Prevalence 25% of baseline and turnout 50% of baseline		£253,460	12.88	9.97	**£19,684**
Prevalence and turnout doubled		£3,937,964	531.50	409.76	**£7,409**
Proportion of HCV viraemic cases doubled	The population prevalence of cleared HCV infection in the study population was much lower than expected.	£1,413,378	144.76	95.16	**£9,764**
Hepatitis B lost to follow up during screening 0%	Previous studies assume different levels of dropout, albeit evidence based on expert opinion. Here we explore values from 0% to 50%, the upper range of Veldhuijzen 's sensitivity analyses	£956,020	131.40	102.40	**£7,276**
Hepatitis B lost to follow up during screening 50%		£1,398,357	102.90	73.91	**£13,589**
SENSITIVITY ANALYSIS OF DISEASE PROGRESSION					
Hepatitis B disease progression	In the base case, we assume that spontaneous case detection carries on in the long term at a similar rate to the control arm of the model initially. We also assume that cases of incipient decompensation present automatically to healthcare services. This has previously been found to be the greatest source of variation in analyses relating to HBV screening.				
Disease progression to cirrhosis 20% of base case		£1,955,824	42.22	13.23	**£46,321**

Disease progression to cirrhosis 50% of base case		£1,472,482	£86.72	57.72	**£16,980**
Initial adult distribution of hepatitis C even across pre-cirrhotic states (base case all patients =F0).	Hepatitis C infection in migrants may well occur earlier than in western populations, so significant disease progression will have occurred by adulthood	£1,134,794	141.36	95.16	**£8,028**
Progression to Liver transplant waiting list	Base case probabilities suggest that many patients with decompensated cirrhosis do not get a transplant. The American Liver Foundation estimates that every year 6,000/17,000 patients who need a transplant get one. Combined with waiting list data, this produces a revised transition from decompensated cirrhosis to waiting list of p-=0.48 per year.	£1,006,166	122.07	92.80	**£8,242**
SENSITIVITY ANALYSES OF DISCOUNT RATES					
Dutch national guidelines for discounts and costs. 1.5% for benefits and 4% for costs	To facilitate comparison of our results with other studies	£1,081,962	197.18	153.90 This equates to 14.0 QALYs per treated patient compared to Veldhuijzen's 13.8	**£5,487**
1.5% for benefits and costs	standard low values	£938,586.44	197.18	153.90	**£4,760**
5% for benefits and costs	Canadian national guidelines.	£1,117,905	91.66	69.18	**£12,196**
COSTS OF SCREENING PROGRAMME	The cost of setting up the programme and recruiting volunteers is a substantial undiscounted cost in the final analysis, and may vary due to costs of procedures and administration costs				
Double costs of screening programme		£2,439,898	124.16	95.16	**£19,651**
Double cost of blood tests		£1,218,280	124.16	95.16	**£9,812**
ESTIMATED COSTS DURING LONG TERM FOLLOW UP					
Cost of liver transplant =halved	Data on the increased cost of liver transplants are relatively recent, and there is considerable variability in the estimates (usually lower) used in previous studies.	£1,079,505	124.16	95.16	**£8,695**
Cost of decompensated cirrhosis management					
Increase cycle cost of decompensated cirrhosis x3	The costs of decompensated cirrhosis management can vary depending on, for example, the number of emergency interventions a patient has. Coffin et al, from a similar base case value, vary the cost over an approximately 3 fold range.	£938,383	124.16	95.16	**£7,558**
Reduce by half	Veldhuijzen et al use a much lower annual cost which equates to approximately half our base case value	£1,096,202	124.16	95.16	**£8,829**
TREATMENT OPTIONS WITH HEPATITIS C					

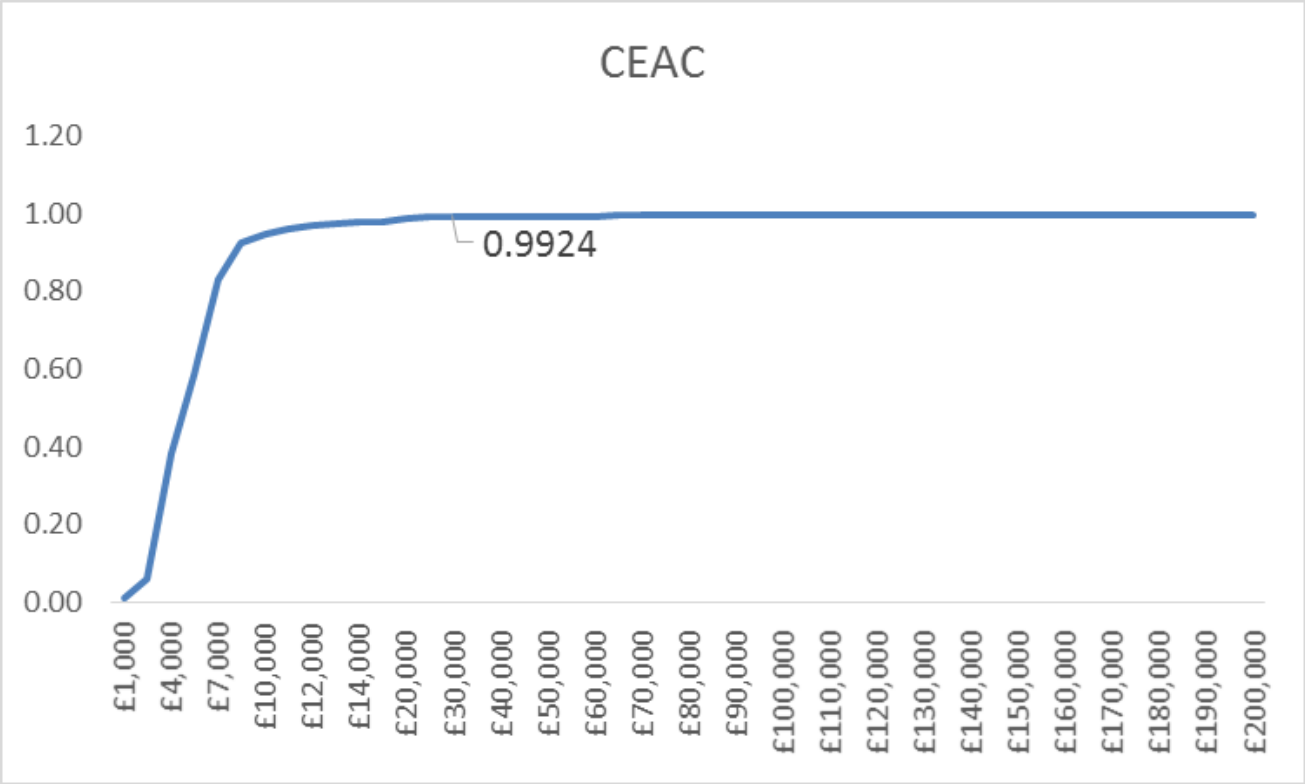
Vary percentage of HCV genotype 3 infected patients achieving SVR with Peg Riba to lower bound of published evidence in Pakistani patients	SVR success = 57%	£1,148,115	124.16	95.16	**£9,247**
Upper bound	SVR success = 75%	£1,022,900	124.16	95.16	**£8,239**
Reduce achievement of SVR to 60% in cirrhotic patients (*sub QALYs is HCV)	Although the efficacy of these drugs is high and some studies report treatment effect for such patients as being comparable with non-cirrhotic patients, this is not definitively established	£952,494	147.40	*52.23	**£6,462**
Treatment of all patients with DAAs at full price, assuming 24 weeks treatment with sofosbuvir/ribavirin for G3		£2,257,765	124.16	95.16	**£18,185**
Discounted to £4800 per G1 treatment course and £10,000 for G3		£1,066,210	124.16	95.16	**£8,587**
For population of G1 patients at above discount (or equivalently, G3 cost = G1)		£976,935	124.16	95.16	**£7,868**
TREATMENT OPTIONS FOR HEPATITIS B					
Treat all hepatitis B patients with Entecavir in long term.	To explore the effect of using more expensive treatment in long term follow up.	£1,111,233	124.16	95.16	**£8,950**
Patients with active disease needing long term treatment = 20%		£981,890	124.16	95.16	**£7,908**
Initial distribution of active HBV cases = all e antigen positive		£1,086,770	121.34	92.35	**£8,956**
Initial distribution of active HBV cases = all e antigen negative		£1,046,416	126.51	97.51	**£8,271**
SENSITIVITY ANALYSIS OF UTILITY VALUES					
Utility CHB = 0.86		£1,060,335	91.94	62.94	**£11,533**
Utility CHB = 0.86 plus compensated cirrhosis = 0.85	As above, plus Eckmann use value of 0.85 for compensated cirrhosis state.	£1,060,335	80.61	51.62	**£13,154**
Utility CHB =0.86 and utility of viral suppression state =0.85	To examine the potential disutility of taking antiviral treatment	£1,060,335	90.12	61.13	**£11,766**

13.11.2 Probabilistic Sensitivity Analysis

Results of our probabilistic sensitivity analysis (figure 15) show that the proposed whole cohort intervention is cost-effective at WTP thresholds below £30,000 per incremental QALY in approximately 99% of simulations (figure 16). In 14/5000 simulations (0.2%) the intervention dominates current practice. These simulations tended to be instances in which the proportion of HBV patients taking antiviral treatment for a prolonged period were very small. In 6/5000 interventions (0.1%) the intervention was less effective than current practice. These simulations tended to be instances where the sampling of parameters relating to progression to hepatocellular carcinoma was such that the progression in known patients with inactive hepatitis B was simulated to be faster than in unscreened patients, a very unlikely scenario in practice. The mean of the PSA was £5,291.82. This is considerably lower than the mean of the deterministic analysis. One reason for this is that the PSA sampling was able to examine the potential outcomes on the result, had the practices which were least successful in recruiting and screening shown similar performance to the most successful ones.

Figure 15 Cost effectiveness plane (WTP threshold of £30,000)

Figure 16: Cost Effectiveness Acceptability Curve



13.12 Summary Points from Cost Effectiveness Analysis

- One off interventional screening is cost-effective at willingness-to-pay (WTP) thresholds in excess of £8,540 per Incremental QALY.
- In the base case this results in 8.65 incremental QALYs per treated case of HBV and 0.81 per treated case of HCV. Allowing for differences in discounting rates, these figures compare closely with recent published models.
- It also results in 13.49 prevented deaths from HBV or HCV, including 5.33 from HCV, (per ~10,000 patients screened).
- 72% of HBV or HCV related deaths appear to be due to HCC.
- The cost of the screening programme was £1,379,563.58, of which £772k (56%) of cost was due to treatments of HCV.
- The result is most sensitive to the mean age of the cohort, disease prevalence, choice of treatment for HCV (see note about pricing below) and cost of the screening programme. In particular, the cost of the initial screening blood tests is very low compared to published studies and may have a degree of influence in other settings. The result also showed some sensitivity to the utility values associated with inactive HBV (but not decision influencing). The result was relatively insensitive to the initial distribution of disease in younger adults, used as a proxy for the age/duration of infection differences that might exist amongst migrants compared to western populations. Other factors that were relatively insignificant included the proportion of HBV e antigen negative cases and the proportion of cases taking long term viral suppression treatment, although this does have a significant influence on the incremental cost.

- A screening programme based on identifying cases in over 40s is cost effective at WTP thresholds in excess of £15,696 per QALY. The mean age of the over 40s in this data was 50. The model predicts that the intervention would cease to be cost effective at NICE WTP thresholds in cohorts with a mean age of 57 or more (based on either whole cohort or over 40 subgroup data).
- A screening programme based on Pakistani ethnicity would be cost effective at WTP thresholds in excess of £9523. Despite the high prevalence of cases in this age group this result is somewhat higher because of the higher number of cases of HCV, and also, the high proportion of cases of genotype 3 in this population. This result takes into account a more aggressive progression of asymptomatic HBV disease to HCC in this ethnic group.
- Treatment of all HCV cases with sofosbuvir/velapatasvir combination for 12 weeks, is cost effective at WTP thresholds in excess of £15,908 per QALY based on full list price of these drugs
- This reduces to £10,412 or £9,395 in the event of 50% or 75% price discounts being obtained.
- Treatment of all HCV cases with glecaprevir/prebentasvir combination is cost effective at WTP thresholds in excess of £10,547 or £16,702 per QALY based on full list price of these drugs, and assuming either 8 week or 16 week treatment courses for all patients. These results assume a conservative 90% achievement of SVR in treatment naïve patients.
- This reduces to £9,316 per QALY in the event of a 75% price discount assuming 8 weeks treatment for all patients. If 98% SVR can be achieved consistently in treatment naïve patients without cirrhosis, this reduces to £9,153.
- (A comparison of hospital vs community treatment based on the study data suggests that hospital treatment is incrementally cost effective at WTP thresholds in excess of £10,518 per QALY based on the assumptions of no set up cost and similar per appointment staffing cost for each patient attended).
- Further analysis by PSA of the primary comparison shows that the mean of 5,000 ICERs generated by random draws of probability distributions is £5,292.
- The intervention was highly likely to be cost-effective at WTP thresholds below £30,000 per QALY (>99%).
- This result is considerably lower than the deterministic mean ICER owing to the fact that the PSA can explore variability in the performance of practices whose engagement with the study was suboptimal on this occasion.
- We present some reflection on the study limitations

13.13 Assumptions and Limitations

- A number of important assumptions and limitations were necessary to conduct this analysis. For reference, we list the most important of these here:
- We assumed that the tendency to turn up for screening was not influenced by any personal suspicion about the patient's disease status.
- The result is clearly sensitive to screening programme set up costs and a substantial component of this is the cost of initial blood tests which were estimated to be somewhat low, but based on quoted costs and including time to take samples.
- The study data was somewhat limited and the outcome is based on small numbers of positive patients. We redress the balance somewhat in the PSA.
- Most western built models of HBV and HCV screening assume that patients are infected in their 20s (lifestyle) whereas immigrants are typically infected much younger. We had no information about how long patients had been infected, but sensitivity analyses of the disease severity of patients aged 18 (= proxy for patients have been infected longer, and on

which we base the presentation of new cases) shows only small effects on the ICER <£1000 per QALY. This only applies to HCV, since the HBV undiagnosed progression data has an initial distribution based on actual data from Dutch immigrants.

- For simplification we did not apply a disutility of treatment, however we show that this only had a small effect upon the result.
- The proportion of deaths due to HCC is potentially influential since these accounted for over 70% of all deaths. We modelled HCC simply in terms of a terminal care process with a high annual mortality, in line with other studies. In practice, some patients may be eligible for curative treatment, however the criteria are very strict.
- For simplification we assumed that patients not diagnosed had a similar utility to healthy people. In fact, as time passes the number of symptomatic patients in this group may increase (more so for HCV as the progression is more linear). However we assume that patients who become symptomatic do not delay in seeking medical help.
- Patients presenting during long term follow up and the proportion of treatable cases thereof is based on previous published data rather than the present study. However the Dutch figures are proportionally very similar to that discovered during the study and are applied to both model arms.

13.14 Conclusions of the cost effectiveness study

We find that a one-off screening programme is cost-effective in the base case at WTP thresholds in excess of £8,540 per QALY. This is well below the preferred NICE WTP threshold of £20,000 or the upper threshold of £30,000. Ethnic specific sensitivity analyses show that for Pakistani populations this threshold is £9,523 and for over 40s the threshold is £15,696. The higher ICER for Pakistanis reflects the fact that there were proportionally more cases of HCV in this population, with a higher treatment cost and lower QALY yield per treated patient. The higher ICER for the older age group is likely to be a reflection of the fact that the number of treatable cases found as populations age decreases. This is because the infection is likely to have been acquired many decades previously, and more highly progressive disease will present at a younger age. Consequently, patients with subclinical disease are likely to be overrepresented in older populations. In addition, the incremental benefits of treatment may accrue many years after initiation of treatment, so that death from natural causes is more likely to occur before these benefits are realised.

The most important parameters in terms of sensitivity are mean age of the screened cohort, prevalence, and intervention cost. We find that systematic reviews of screening studies have not discussed the importance of the age of the population, partly because such analyses are not common in individual studies. We feel that this parameter has been considerably underestimated in previous reports and further studies in this area are warranted. Conclusion
One off screening of immigrant populations is cost-effective at WTP thresholds of £8,540 per incremental QALY or more, or potentially commencing at £9,153 per QALY if HCV patients can be effectively cured using DAAs at a generous price discount. The cost per QALY is marginally increased in Pakistani populations, and cost effective at less than the higher NICE WTP threshold in populations with mean ages below the mid-50s. Further analysis compensating for the poor recruitment performance of some GP practices suggest that the intervention could be cost effective at WTP thresholds in excess of £5,292 per QALY, and overall, that the intervention is highly likely to be cost-effective at WTP thresholds below £30,000 per QALY.

14. Conclusions

HepFREE was designed to address some of the issues around testing immigrants for chronic viral hepatitis. Our qualitative studies examined background knowledge of viral hepatitis in immigrant communities. We found considerable misinformation about these conditions with clear confusion about symptoms and modes of transmission. Information campaigns focussing on these issues are likely to be required to increase testing rates in these communities. To our initial surprise a 'targetted' information leaflet did not encourage participation in testing but review of the reasons for lack of engagement from our focus group work suggests that the major reason for low screening rates in immigrant communities is the focus on other activities (chiefly employment) and the lack of ready access to healthcare professionals that can communicate in the same language. Testing campaigns led by local advocates who speak the appropriate language and involve testing at multiple 'out of hours' events are likely to be required to improve testing rates in immigrant groups.

Current NICE guideline recommend testing of high risk individuals (including immigrants) for viral hepatitis. In our 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 active practices who were incentivised to participate was much greater with 20% of registered patients undergoing testing whilst only 12.8% of new registrants were tested. Work is now under way to examine characteristics of successful and unsuccessful practices to enable more informed advise regarding the most appropriate way to improve testing for viral hepatitis. Testing rates differed by ethnic group with people from Pakistan likely to participate in screening and we noted an important difference in attendance 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 combined with the cost effectiveness analysis suggest that screening may be more productive if it is focussed on older individuals. An important question addressed by HepFREE was the effectiveness of testing in an area of low prevalence. We noted a marked reduction in screening in our chosen area of low prevalence, perhaps suggesting that more resources and incentives will be required to improve immigrant screening in areas where they are uncommon. However given that only one low prevalence area was included this outcome should be regarded with caution and data from other low prevalence areas are required before firm conclusions can be drawn.

The overall prevalence of viral hepatitis was 2% but a majority of patients with hepatitis C had cleared virus. It is not clear whether this is due to higher rates of viral clearance in elderly, healthy immigrants 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.

We had intended to conduct an integrated study of community treatment vs standard treatment. However arranging therapy with expensive drugs in busy community clinics proved much more challenging than planned with multiple logistical problems delaying initiation of the programme. Patients who were identified and asked to wait until community treatment could be arranged were not willing to delay therapy and this difficulty, along with reluctance to consent to community treatment and the incremental availability of all oral treatments for hepatitis C during the trial, prevented a fully powered study being completed. However it is clear from our data that compliance with medical advise in immigrants screened in primary care is excellent and attendance at hospital clinics is not problematic with excellent attendance rates. Although the study did not meet its calculated recruitment target it is clear that engagement with hospital based treatment is excellent and there are unlikely to be any compliance benefits to community treatment in this cohort. Given the extra costs of community based treatment and the very significant logistical difficulties we do not recommend this approach.

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 immigrant 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 compliance. This is particularly marked for people over the age of 40. We recommend that such testing be introduced without delay and we suggest that a standard invitation letter is all that is required and treatment in a hospital setting is adequate. In areas of low immigrant density the benefits of testing are less clear and studies to improve uptake and cost effectiveness in these communities is required.

15. APPENDICES

15.1 Appendix 1 - PROTOCOL

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:
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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

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1. Introduction

1.1 Background

Chronic viral hepatitis is common in people born outside the UK and involves persistent infection with either hepatitis B or hepatitis C virus. The disease can cause asymptomatic disease that leads to cirrhosis or potentially hepatocellular carcinoma as well as death in a large proportion of those who are infected.

Hepatitis C virus is a blood borne single strand RNA virus which exists in a number of different genotypes. Chronic infection (defined as infection for more than 6 months) is usually asymptomatic and patients usually remain unaware that they are infected until the disease has progressed. However, disease progression and severity is highly likely.

Hepatitis B is a blood borne DNA virus that may also be transmitted sexually or by materno-fetal transmission. Chronic HBV is defined by the presence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection. The disease persists in a number of different, convertible phases. The two major phases are defined by the presence or absence of the hepatitis B e antigen (HBeAg) in the circulation.

These often asymptomatic diseases require multifaceted diagnostic testing, which includes serial testing for antibodies, RNA/DNA as well as liver function tests to ensure patients are accurately diagnosed.

The prevalence rate of viral hepatitis currently stands at approximately 0.5% within the UK. However, statistics for first and second generation immigrants from 'at risk' countries indicates a higher prevalence, perhaps approaching 5%. Current data relating to immigrant populations within the UK is limited. However, it is believed that 7 million first and second generation immigrants from high prevalence countries currently reside in the UK. It is believed that certain 'at risk' communities have a prevalence level similar to their country of origin, as demonstrated by studies conducted in the Somali community in Liverpool as well as the Pakistani community in London, (Brabin *et al.*, 2002 and Uddin *et al.*, 2010). Hence the prevalence of viral hepatitis is at least ten fold greater in immigrants than in the indigenous community.

The UK has one of the lowest rates of therapy for viral hepatitis in Europe and this is undoubtedly contributing to the observed rising mortality from liver disease in the UK. This is, in contradistinction to the rest of Europe, where mortality from liver disease is decreasing. Previous UK studies have shown that access to therapy for patients known to

have viral hepatitis is poor with only a tiny minority of diagnosed patients going on to receive treatment.

Current statistics indicate that of the total UK population that have been infected with hepatitis C, only 17% have been diagnosed and less than 2% go on to receive treatment (Ryder., S, 2004). Hepatitis B is known to be the cause of 50% of primary liver cancer cases within the UK, in which patients are 100 times more likely to develop hepatocellular carcinoma than those who are not infected. Strategies culminating in improved access to treatment are thought likely to have a major impact on treatment uptake and to reduce morbidity. However, currently alternatives to hospital based treatment have not been studied.

Current data indicates that approximately 25% of those with chronic viral hepatitis will die in their fifth decade as a result of their infection, indicating that up to 50,000 immigrants living in the UK may develop cirrhosis and/or liver cancer. The subsequent care of patients with these conditions will add a significant financial burden to the NHS. Further analysis of the current demographics of the immigrant population shows that over 80% are less than 50 years old (Foster, G – unpublished data). It is therefore anticipated that there will be a sharp rise in the number of immigrant deaths associated with viral hepatitis over the coming decade.

Therapy for chronic viral hepatitis is available and is clinically and cost effective as indicated by NICE approval. For chronic HCV infection therapy involves a combination of a long acting interferon combined with ribavirin and, increasingly a direct acting antiviral agent (such as telaprevir or boceprevir). For chronic HBV infection a number of different treatment options are available including interferon based immunomodulatory regimes or perpetual viral suppression with a third generation nucleotide derived antiviral agent, either entecavir or tenofovir. The current model of care involves specialist centres with highly trained staff administering therapy at some distance from the patient's home.

Given the poor uptake of antiviral therapy under current conditions it has been suggested that alternative treatment models should be developed but these have not been assessed or tested in a large scale.

2. Trial Objectives and Design

2.1 Trial Objectives

The central objective of the study is to determine whether screening for chronic viral hepatitis in immigrants living in the UK by testing all registered immigrants in GP surgeries is feasible, effective, and cost effective.

We will examine the costs and benefits of screening compared to current 'standard practice' and evaluate whether an enhanced patient information invitation letter (as opposed to 'standard patient information invitation letter') enhances engagement as well as determining whether local delivery of therapy improves 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'.

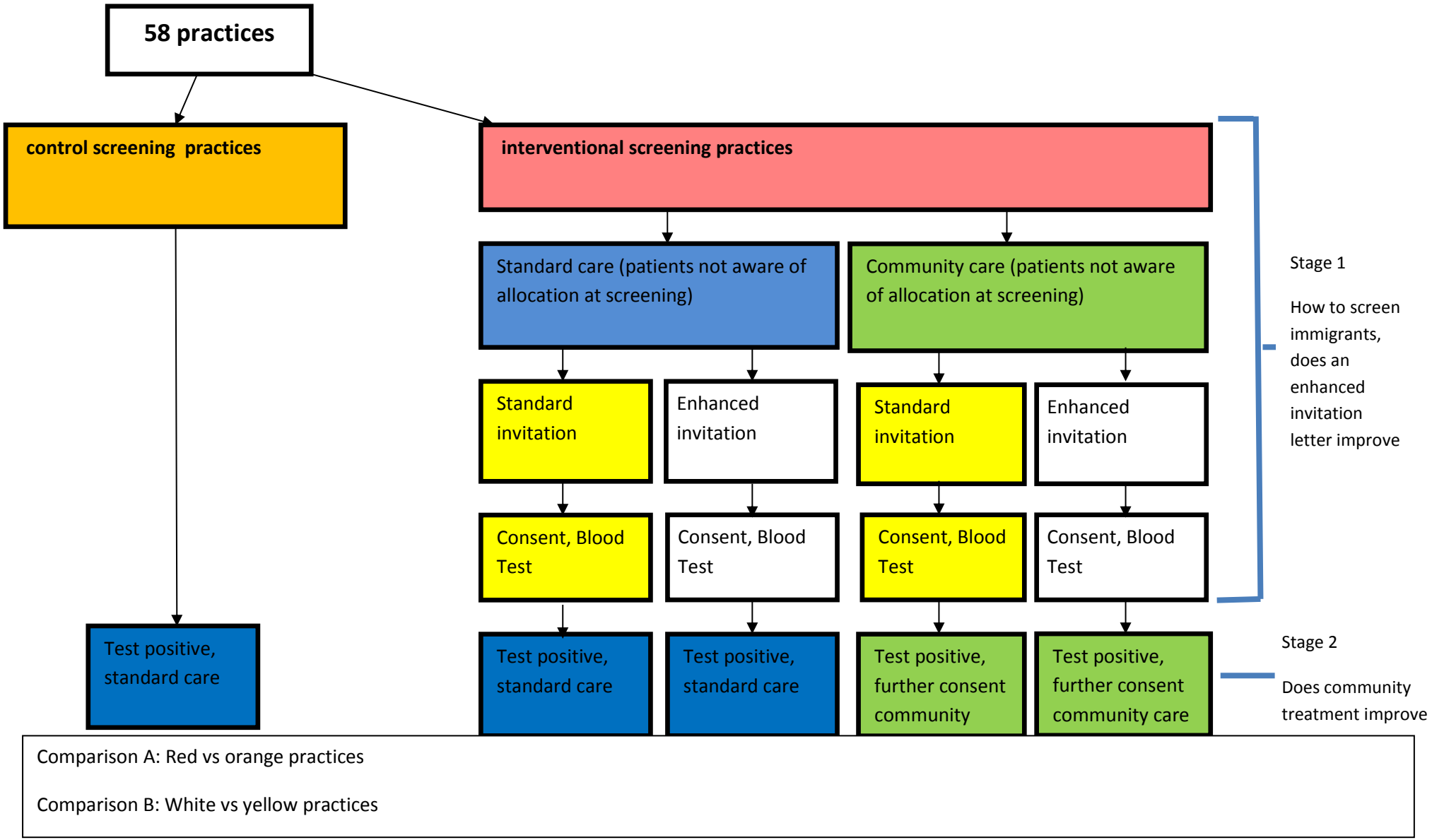
2.2 Trial Design

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



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 Proivder 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, ie all individuals on whom we have outcome data.

Baseline comparisons of both cluster and individual characteristics will be presented. We will report separate analyses using generalized estimating equations for the main analyses for our three comparisons as follows:-

7.3 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 SystemOne, by a HepFree specific template. Only authorized personnel will have access to the EMIS/SystemOne database at the practice level. Data relating to the primary outcome will be collected in an identical way between control and intervention practices. In intervention practices data from participants who have agreed to share personal data with the trial team will be included in the cost effectiveness analysis.

Data files containing HepFree specific data will be transferred from the GP practices to the HepFree data management team via a method deemed secure and in accordance to information governance policy.
Once HepFree data files are securely received by the data manager they will be uploaded onto a dedicated folder on the secure virtualised environment at the Barts Cancer Centre (BCC). This is where all data analysis of PCTU trial data is carried out. The BCC environment requires a two factor authentication to access the portal via Citrix and the folders where the data is stored are only accessible to the appropriate members of the PCTU and HepFree trial team.

The data files will be imported into a template Access database, within the BCC network, where various data integration steps will be performed to remove any duplication, standardise and ensure data quality.

For Stage 2 of the trial, trial specific data will be collected using Case Report Forms within an electronic data capture program hosted by a secure online data management system called OpenClinica. The CRFs can be accessed via an encrypted and secure uniform resource locator (URL) using a unique username and password, which is externally validated, and the details of the validation will be held in electronic files by the PCTU. Only authorised members of the HepFree team, who are fully trained, will be granted user accounts. A full audit trail will be accessible to data managers at the PCTU and relevant members of the HepFree team. The OpenClinica software is provided by OpenClinica and is hosted on a server by their hosting partner in the UK.
The trial statistician will receive a fully integrated dataset which is blinded to GP trial allocation and GP location (South or East London or Bradford).

For the Pre-screening survey paper questionnaires will be used in the first instance. Data from these questionnaires will be entered into an OpenClinica database in the same way as described for Stage 2 of the trial above. The electronic survey will be designed to mirror the paper survey to ensure data is transferred accurately. 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 the reasons for the urgent safety measures and the plan for future action.	Main REC and Sponsor Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination)	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor

		The end of study should be defined in the protocol		
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

- Algeria
- Egypt
- Libyan Arab Jamahiriya
- Morocco
- Tunisia

East Africa

- Burundi
- Comoros
- Djibouti
- Eritrea
- Ethiopia
- Kenya
- Madagascar
- Malawi
- Mauritius
- Mozambique
- Reunion
- Rwanda
- Seychelles
- Somalia
- Uganda
- United R. of Tanzania

Southern Africa

- Botswana
- Lesotho
- Namibia
- South Africa
- Swaziland
- Zimbabwe

West Africa

- Benin
- Burkina Faso
- Cape Verde
- Cote d'Ivoire
- Gambia
- Ghana
- Guinea
- Guinea-Bissau
- Liberia
- Mali
- Mauritania

- Niger
- Nigeria
- Sao Tome and Principe
- Senegal
- Sierra Leone
- Togo

Central Africa

- Angola
- Cameroon
- Central African Republic
- Chad
- Congo
- D. R. of the Congo
- Equatorial Guinea
- Gabon
- Sudan
- Zambia

Europe

Eastern Europe and the Newly Independent States of the former Soviet Union

- Albania
- Armenia
- Azerbaijan
- Belarus
- Bosnia and Herzegovina
- Bulgaria
- Croatia
- Czech Republic
- Estonia
- Georgia
- Kazakhstan
- Kyrgyzstan
- Latvia
- Lithuania
- Poland
- Republic of Moldova
- Romania
- Russian Federation
- Slovakia
- Tajikistan
- T.F.Y.R. Macedonia
- Turkmenistan
- Ukraine
- Uzbekistan
- Yugoslavia

Western Europe

- Greece
- Italy
- Malta
- Portugal
- Spain

The Americas

Mexico and Central America

- Belize
- Guatemala
- Honduras
- Panama

Temperate South America

- Argentina

Tropical South America

- Bolivia
- Brazil
- Ecuador
- Guyana
- Suriname
- Venezuela

The Caribbean

- Antigua and Barbuda
- Dominica
- Dominican Republic
- Grenada
- Haiti
- Jamaica
- Puerto Rico
- Saint Kitts and Nevis
- Saint Lucia
- St Vincent & Grenadines
- Trinidad and Tobago
- Turcs and Caicos Islands

Australia and the South Pacific Islands

- American Samoa

- C.N. Mariana Islands
- Cook Islands
- Fiji
- French Polynesia
- Guam
- Kiribati
- Marshall Islands
- Micronesia
- Nauru
- New Caledonia
- Niue
- Palau
- Papua New Guinea
- Samoa
- Solomon Islands
- Tonga
- Tuvalu
- Vanuatu
- Wallis and Futuna Islands

Asia

East Asia

- China
- D. People's R. of Korea
- Japan
- Mongolia
- Republic of Korea

Middle East

- Bahrain
- Iran (Islamic Republic of)
- Iraq
- Israel
- Jordan
- Kuwait
- Lebanon
- Oman
- Qatar
- Saudi Arabia
- Syrian Arab Republic
- Turkey
- United Arab Emirates
- Yemen

Southeast Asia

- Brunei
- Cambodia
- Indonesia
- Lao People's D. R.
- Malaysia
- Myanmar (Burma)
- Philippines
- Singapore
- Thailand
- Vietnam

Indian Subcontinent and South Asia

- Afghanistan
- Bangladesh
- Bhutan
- India
- Maldives
- Nepal
- Pakistan

15.2 Changes to the protocol HepFREE 1

Version Number	Version Date	REC Submission/Approval Dates	CSP Submission/Acknowledgment Dates	Summary of changes (document if substantial or non substantial)
1.0	20Sep12	Submitted : 17Oct12	-	
1.1	29Oct12	Submitted : 31Oct12 Full Approval not given – Conditional approval given (v2.0 to address the conditions issued by the REC)	Uploaded onto IRAS on 01Nov12	Non substantial: There was a noted minor discrepancy in between the ethics IRAS application and the submitted protocol (v1.0 dated 17Oct12). Ethics was contacted and allowed the typos to be corrected accordingly. The protocol was amended and re-sent to ethics prior to the ethics meeting (please see section X of the TMF for further _orrespondence)
2.0	05Dec12	Submitted: 14Dec12 Approved 24Dec12	Submitted:02Jan13	Non substantial: The REC issued some minor changes (change study title) that needed to be met in order for full approval to be given. Further typos were addressed at this time.
2.1	22Feb13	Submitted: 15Mar13 Approved: 28Mar13	Submitted: 15Apr13	Substantial: There was a change of sponsorship from BH to QM, with some minor clarifications to the body of text
2.2	23May13	Submitted: 23May13 Acknowledged:24May13	Submitted :28May13	Non substantial – CSP global checks addressed some typos and queried insurance wording on PIS – after discussion with R&D – this was approved to be submitted as a non substantial amendment.
3.0	01Jul13	Submitted: 15 Aug13 Acknowledged: 09Sep13 Approved:	Submitted:	Substantial – The inclusion of a sub-study that has a pre-screening component as well as the inclusion of the augmented screening invitation letter as well as amending the standard invitation letter. Removal of DNA components.
4.0	03Dec13	Submitted: 20 Feb14 Acknowledged: 20Feb14 Approved: 12Mar14	Submitted: 03Mar14	Substantial - This substantial amendment relates to the substantial changes in the Patient Information Sheet for the screening portion. The current standard practice is that if someone tests positive for HepB/C, all immediate family members which includes children are recommended to get tested. It is thus felt that it is important to try and establish the resulting testing rate within this demographic by the collation of statistical data with both authorisation from the parental guardian as well as the custodian of the data (ie the GP practice)
5.0	09Mar14	Submitted: 24Apr14 Acknowledged: 06May14 Approved: 14May14	Submitted:18May2014	Substantial - This substantial amendment relates to the substantial changes in the research methodology of the protocol as well as assessing the effects of the local awareness campaign to be set by local community groups.
6.0	27Jun14	Submitted: 07Aug14 Acknowledged: 07Aug14 Approved:22Aug14	Submitted: 07Aug14	Substantial - This substantial amendment relates to the substantial changes in the research methodology of the protocol (Change to study nos and site nos due to revised power calculation due to revised forecast eligible patients)
6.1	16Dec14	Submitted:23Dec14	Submitted: ~Dec14	Non-substantial – The minor amendment corrects typos and minor inconsistencies

		Acknowledged:30Dec14 Approved:30Dec14	**Awaiting confirmation**	within the text of both the Protocol and Patient Information Sheet.
7.0	12Mar15	Submitted:12Mar15 Acknowledged:21Apr15 Approved:05May15	Submitted: 14May15 Re-submitted 17Jun15	Substantial – The substantial amendment contains a number of minor modifications to the layout of the Protocol to improve readability and comprehension. Also included: - A modification to the supplementary consent form for patients that are found to be positive for viral hepatitis and how consent is sought - Definition of 'engaged' - Modification to the way researchers access results from the study - Update to the main Participant Information Sheet and Consent Form

15.3 Changes to the protocol HepFREE2

	Protocol version	Protocol date	Minor or substantial amendment	Date approved by Ethics	Date approved by MHRA	Date approved/ acknowledged by R&D	Date implemented	PIS/ consent version and date	Comments and description
Initial version	1.0	05 Sept 2012	N/A	30 July 2012	30 July 2012	30 July 2012	05 Sept 2012	2.0 05 Sept 2012	
1st amendment	1.1	13 Aug 2013	Minor	09 Aug 2013	09 Aug 2013	09 Aug 2013	13 Aug 2013	2.2 05 Sept 2013	Minor text changes within the text relating to indemnity in the protocol and the screening patient information sheet.
2nd amendment	V 3.0	07 May 2015	Substantial	10 Apr 2015	10 Apr 2015	10 Apr 2015	07 May 2015	2.2 05 Sept 2013	Changes to the research methodology and design to bring it more in line with the high prevalence screening interventional study (HepFree). Changes to accompanying study literature, including removal of the augmented

	Protocol version	Protocol date	Minor or substantial amendment	Date approved by Ethics	Date approved by MHRA	Date approved/ acknowledged by R&D	Date implemented	PIS/ consent version and date	Comments and description
									screening invitation letters
3rd amendment	V 4.0	05 Sept 2016	Substantial	05 Sept 2016	05 Sept 2016	05 Sept 2016	05 Sept 2016	2.2 05 Sept 2013	Revised sample size calculation due to a higher number of eligible patients per practice than initially anticipated. Also inclusion of two exploratory analyses.

15.4 Appendix 2 Invitation Letters

HepFREE – Augmented invitation letter

[GP surgery address/ headed notepaper]

Dear [Name of patient],

We are writing to tell you that your GP surgery is working on a new project with a research team from Queen Mary University of London. **The aim of the project is to encourage more people in London and Bradford to get a free test for Hepatitis B and Hepatitis C**. These are viruses that can affect the liver and may need treatment. It is very important that the Hepatitis B and C viruses are found and treated early, so that people can live a longer and healthier life. Your GP surgery and the research team hope to test people for Hepatitis B and C, so that we can offer advice and free treatment to people who test positive for Hepatitis B/C.

We would like to offer you the opportunity to have a free, simple blood test for Hepatitis B and C organised by your GP surgery. Receiving this letter does **not** mean that the GP thinks you are ill. Many other people from the GP surgery have also received this letter and have been offered the test. **We hope as many people as possible will take this opportunity for an important free health check.**

If you agree to have a Hepatitis B/C test, this will **involve a 10 minute visit to your GP surgery**. The GP will discuss hepatitis with you and organise the test. The test will draw a small amount of blood from your arm and this blood will only be tested for Hepatitis B/C.

Included on the back of this letter is an information sheet to tell you more about Hepatitis B and C. **If you would like to talk about the project further or ask questions please contact the GP surgery**. A member of the team may contact you to see if you would like to book an appointment to take part in the project, or you can call or attend your GP surgery. You can leave this project whenever you want without giving a reason and this will not affect your medical care.

Yours sincerely,

_____ _____

GP HepFree/QMUL

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.**

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.

HepFREE – Standard invitation letter

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

Parameter	Distribution	Parameter name or description	Parameter 1(P1)	Parameter 2	Mean value	Source
Input screening numbers						
Number invited	BETA	Alpha, beta.			47,529/58,512	HepFree trial data
Number screened	BETA	Alpha, beta.			11,386/47,529	HepFree trial data
Number receiving blood test	BETA	Alpha, beta.			10,524/11,386	HepFree trial data
N_HBV positive	Sum of Binomial, practice level	N,p	N cases per found per practice	N tested per practice	No single value, aggregate of 50 practices	HepFree trial data
N_HCV positive	Sum of Binomial, practice level	N,p	N cases per found per practice	N tested per practice	No single value	HepFree trial data
Proportions						
P_HBV_population	Beta	Parameterised in terms of case finding	Number of cases found in tested population	Unaffected individuals in tested population	115/10524	HepFree trial data
P_HCV_population	Beta		Parameterised in terms of case finding	Number of cases found in tested population	105/10524	HepFree trial data
P_HCV genotype=x	Beta	Alpha, Beta			P_HCV3 = 0.83 P_HCV1 =0.07	HepFree trial data

			P_HCV4=0.09	
P_fibroscan or biopsy performed | patient has HBV or HCV	Beta	Alpha, Beta	P_fibroscan b = 91/115 P_biopsy B = 5/115 P_fibroscan C =30/36 P_biopsy C =17/36	HepFree trial data
P_treatment received | patient has HBV or HCV			P_treat tenofovir =4/10 P_treat entecavir =3/10 P_treat_other =3/10 P_treat Simeprevir combination =1/36 P_treat sofosbuvir combinations =13/36 P_treat PegRiba =22/36	HepFree trial data
P_SVR| treated with pegylated interferon/ribavirin	Binomial	N,p	P = 0.69 for over 40s SVR range of 0.57-0.75	Aziz et al[37] Waheed et al[38]

Transition probabilities				
TRANSITION FROM:	Log normal using quoted intervals as 95% CI	Mean	Range	
From inactive CHB, HBsAg-positive	To Seroclearance <30 years	0.8	(0.38-1.15)	Toy et al 2014[32]
From inactive CHB, HBsAg-positive	30-39 years	1.1	(0.53-1.60)	Toy et al 2014
From inactive CHB, HBsAg-positive	40-49 year	1.7	(0.82-2.47)	Toy et al 2014
From inactive CHB, HBsAg-positive	50+ years	1.8	(0.91-2.74)	Toy et al 2014
From inactive CHB, HBsAg-positive	To active CHB, HBeAg-positive <30 years	0.9	(0.4-1.3)	Toy et al 2014
From inactive CHB, HBsAg-positive	30-39 years	1.4	(0.7-2.1)	Toy et al 2014
From inactive CHB, HBsAg-positive	40-49 years	2.8	(1.4-4.1)	Toy et al 2014
From inactive CHB, HBsAg-positive	50+ years	2	(1.0-3.0)	Toy et al 2014
From inactive CHB, HBsAg-positive	To cirrhosis <30 years	0.038	(0.019-0.057)	Toy et al 2014
From inactive CHB, HBsAg-positive	30-39 years	0.049	(0.024-0.073)	Toy et al 2014
From inactive CHB, HBsAg-positive	40-49 years	0.068	(0.034-0.102)	Toy et al 2014
From inactive CHB, HBsAg-	50+ years	0.15	(0.052-0.202)	Toy et al 2014

positive				
From inactive CHB, HBsAg-positive	To HCC All ages	0.168	(0.001-0.25)	Toy et al 2014
From active CHB, HBeAg-positive				
From active CHB, HBeAg-positive	To seroconversion All ages	7	(2.0-23)	Toy et al 2014
From active CHB, HBeAg-positive	To active CHB, HBeAg-negative All ages	1.9	(1.0-3.8)	Toy et al 2014
From active CHB, HBeAg-positive	To cirrhosis All ages	2.4	(2.1-2.6)	Toy et al 2014
From active CHB, HBeAg-positive	To HCC All ages	0.8	(0.5-1.0)	Toy et al 2014
From active CHB, HBeAg-positive	To HBV-related death All ages	0.6	(0.2-0.9)	Toy et al 2014
From active CHB, HBeAg-negative	To inactive CHB, HBsAg-positive All ages	1.6	(0.0-11)	Toy et al 2014
From active CHB, HBeAg-negative	To cirrhosis All ages	2.4		Toy et al 2014
From active CHB, HBeAg-negative	To HCC All ages	0.8	(0.5-1.0)	Toy et al 2014
From active CHB, HBeAg-negative	To HBV-related death All ages	0.6	(0.2-0.9)	Toy et al 2014
From active CHB, HBeAg-negative	From seroconversion			Toy et al 2014
From active CHB, HBeAg-negative	To active CHB, HBeAg-negative <30 years	2.9	(1.4-4.3)	Toy et al 2014
From active CHB, HBeAg-	31-40 years	3.8	(1.9-5.7)	Toy et al 2014

negative				
From active CHB, HBeAg-negative	40+ years	8.6	(4.3-12.9)	Toy et al 2014
From active CHB, HBeAg-negative	To cirrhosis <30 years	0.2	(0.1-0.3)	Toy et al 2014
From active CHB, HBeAg-negative	31-40 years	1	(0.5-1.5)	Toy et al 2014
From active CHB, HBeAg-negative	40+ years	4.2	(2.1-6.3)	Toy et al 2014
From active CHB, HBeAg-negative	To HCC <30 years	0.1	(0.05-0.15)	Toy et al 2014
From active CHB, HBeAg-negative	31-40 years	0.2	(0.1-0.3)	Toy et al 2014
From active CHB, HBeAg-negative	40+ years	0.6	(0.3-0.9)	Toy et al 2014
From active CHB, HBeAg-negative	To seroclearance <30 years	0.8	(0.4-1.2)	Toy et al 2014
From active CHB, HBeAg-negative	31-40 years	0.7	(0.3-1.0)	Toy et al 2014
From active CHB, HBeAg-negative	40+ years	0.3	(0.1-0.4)	Toy et al 2014
From active CHB, HBeAg-negative	From seroclearance			Toy et al 2014
From active CHB, HBeAg-negative	To HCC 50+ years	1	(0.0-2.0)	Toy et al 2014
From cirrhosis				Toy et al 2014
From cirrhosis	To decompensated cirrhosis All ages	3.9	(3.2-4.6)	Toy et al 2014
From cirrhosis	To HCC All ages	5	(3.0-7.0)	
From cirrhosis	To HBV-related	5.6	(3.1-8.0)	Toy et al 2014

	death All ages				
From cirrhosis	From decompensated cirrhosis				Toy et al 2014
From cirrhosis	To liver transplantation * All ages	12	(6.0-18.0)		Toy et al 2014
From cirrhosis	To HCC All ages	7.1	(3.5-10.0)		Toy et al 2014
From cirrhosis	To HBV-related death All ages	15	(9.9-20.0)		Toy et al 2014
From HCC	To liver transplantation * All ages	4.7	(2.3-7.0)		Toy et al 2014
	To HBV-related death All ages	54.5	(20.0-60.0)		Toy et al 2014
From liver transplantation	To HBV-related death All ages	6.6	(2.0-12)		Toy et al 2014
Hepatitis C transitions					
From	**To**	**Base Value**	**Low**	**High**	**Source**
F0	F1				Thein et al[35]
Study setting:	Liver clinic				Thein et al
	0.116	0.098	0.123		Thein et al
	Age >=40 years	0.110	0.102	0.129	Thein et al
	Studies published since year 2000	0.115	0.062	0.246	Thein et al
	Community studies	0.124	0.103	0.131	Thein et al
					Thein et al
F1	F2				Thein et al
Study setting	Liver clinic				Thein et al

	0.082	0.071	0.094		Thein et al
	Age >=40 years	0.079	0.069	0.090	Thein et al
	Studies published since year 2000	0.083	0.073	0.094	Thein et al
	Community studies	0.073	0.048	0.110	Thein et al
F2	F3				Thein et al
Study setting	Liver clinic				Thein et al
	0.119	0.106	0.133		Thein et al
	Age >=40 years	0.116	0.104	0.129	Thein et al
	Studies published since year 2000	0.115	0.104	0.127	Thein et al
	Community studies	0.123	0.082	0.185	Thein et al
F3	Compensated cirrhosis F4				Thein et al
Study setting	Liver clinic				Thein et al
	0.117	0.104	0.132		Thein et al
	Age >=40 years	0.113	0.100	0.128	Thein et al
	Studies published since year 2000	0.112	0.100	0.125	Thein et al
	Community studies	0.165	0.126	0.217	Thein et al
Compensated cirrhosis F4	Decompensated cirrhosis(Dc)	0.0390	0.0300–	0.0480	Coffin et al 2012[39]
DC	Transplant waiting list	0.0310	0.0248	0.0372	Coffin et al 2012
Waiting list	Transplantation	0.71			NHS England annual report on

					liver transplantation 2016
F3	HCC	****			Coffin et al 2012
F4	HCC	0.0190	0.0170	0.0550	Coffin et al 2012
DC	HCC	0.0140	0.0060	0.0200	Coffin et al 2012
F4 SVR	relapse	****			Coffin et al 2012
DC	DEATH	0.1290	0.1032	0.1548	Coffin et al 2012
HCC	DEATH	0.4270	0..3416–	0.5124	Coffin et al 2012
Transplantation	DEATH year 1	0.135			McEwan et al 2013[40]
Transplantation	DEATH yr 2 onward	0.03			McEwan et al 2013
Utilities	Normal	Mean, SE			
Hepatitis B					
Undetected Hepatitis B[1]			0.95	0.01	Levy et al[31]
Seroclearance[1]			0.95	0.01	Levy et al
Viral suppression[1]			0.95	0.01	Levy et al
Chronic inactive disease[1]			0.95	0.01	Levy et al
Active disease, e positive			0.85	0.01	Levy et al
Active disease, e negative			0.85	0.01	Levy et al
Compensated cirrhosis			0.69	0.01	Levy et al
Decompensated cirrhosis			0.35	0.01	Levy et al
Post-transplant surgery			0.67	0.01	Levy et al
HCC			0.38	0.01	Levy et al
Hepatitis C					
Seroclearance/SVR			0.82	0.0005	Castelnuovo et al[22]
Undetected			0.79	0.024	Castelnuovo et al
F0			0.75	0.024	Castelnuovo et al
F1			0.75	0.024	Castelnuovo et al

F2	0.75	0.024	Castelnuovo et al
F3	0.75	0.024	Castelnuovo et al
Compensated cirrhosis	0.55	0.054	Castelnuovo et al
Decompensated cirrhosis/HCC	0.45	0.056	Castelnuovo et al
Post-transplant surgery	0.67	0.067	Castelnuovo et al

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