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Title: A cluster randomised trial of case finding and therapy for chronic viral hepatitis in primary care (HepFREE).

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Abstract: Background

The prevalence of chronic viral hepatitis is >2% in low and middle income countries but lower in high income countries. Migrants to high income countries are more likely than their hosts to be infected, and usually live in circumscribed areas. The best way to find and treat such people, both in high and low migrant density areas, is unknown.

Methods

HepFREE was a cluster randomised controlled clinical trial in 90,250 subjects examining the hypothesis that incentivising and supporting primary care physicians increases screening rates for viral hepatitis in migrants in areas of high immigrant density (Bradford, Yorkshire and London (North and South East)). In nested sub-studies we examined whether bespoke invitation letters were beneficial and whether community care increased engagement. We conducted a parallel investigation of screening in a region of low migrant density (Oxford).

Findings

The intervention (incentivised general practitioners) increased screening from 1.7% to 19.5% (IRR = 3.7, $p = 0.01$) and was cost effective. A bespoke invitation letter did not increase uptake. Community care did not improve engagement, with > 85% participant attendance at both standard hospital and community care appointments. In a low immigrant density area the screening rate by incentivised doctors was 7.5%. Overall the prevalence of chronic viral hepatitis in people identified in primary care as originating from a country with a high prevalence was 2% (1% HBV, 1% HCV) but only 32% of patients testing positive for hepatitis C antibodies were viraemic.

Interpretation

Screening immigrants for viral hepatitis in primary care is effective if doctors are incentivised and supported. Community care is expensive and there is no evidence that this offers benefits in this setting or that bespoke invitation letters add value. The prevalence of patients with hepatitis C viraemia is lower than previously reported.

Funding and registration
NIHR Programme Grant, ISCRTN 54828633

A cluster randomised trial of case finding and therapy for chronic viral hepatitis in primary care (HepFREE).

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Background

Chronic infection with the hepatitis B or hepatitis C virus (HBV, HCV - referred to as “viral hepatitis” henceforth) is common, with several hundred million people infected worldwide¹. Viral hepatitis is common in low and middle income countries (LMICs) where materno-fetal transmission (HBV) and use of poorly sterilised medical equipment (HCV) have led to high prevalence with substantial morbidity (e.g. West Africa where HBV may affect up to 15% of the population² and Pakistan where HCV prevalence in some regions may exceed 20%³). In many high income countries (HICs) the prevalence of viral hepatitis is <1% and infection is common only in those with a history of injecting drug use, for whom screening is encouraged⁴. Effective therapy is available – all oral therapy for HCV clears the virus in >90% of those treated⁵⁻⁷ and long-term suppression of HBV replication with oral nucleosides prevents complications and can reverse cirrhosis^{8,9}. Given the mortality associated with untreated viral hepatitis and the benefits of therapy, the WHO has recommended that testing and treatment for these infections should be scaled up with the goal of reducing their impact by 2030.

Community studies confirm that the prevalence of viral hepatitis in migrants is higher than among the general population in many HICs¹⁰⁻¹². However, immigrants are rarely prioritised for health care interventions and treatment rates following community screening has been low¹⁰. It is unclear how best to screen and engage with at-risk immigrants, and it is unknown whether those registered with primary care physicians can be identified, tested, and treated. Migrants are not evenly distributed and usually concentrate in inner city locations. It is unknown whether testing in areas of low migrant density is effective. HepFREE addressed these issues and determined whether routine testing – screening - for viral hepatitis in primary care in high and low migrant density areas was worthwhile.

Methods

Trial design

HepFREE investigated the hypothesis that incentivising general practitioners (GPs) to test migrants (identified by searches of electronic records) for viral hepatitis is superior to ad hoc testing and is cost effective. A cluster design was chosen to minimise training and spill over-effects. Clusters consisted of all migrant patients registered at a practice (or a random subset of such patients) and interventions were delivered at cluster level in parallel interventions. Patients registered with the practice were not informed of the allocation but the practices were aware. Trial randomisation was performed using biased coin randomisation. The programme managing allocations was web-based, developed using Java at Queen Mary University London. Patients did not consent to participate in the trial but gave informed written consent to be tested and have data collected.

The trial took place in Bradford, Yorkshire, South East and North East London, chosen as areas of high migrant density. The trial compared standard screening (in which GPs were given a teaching session on viral hepatitis and asked to test migrants registered with their practice) to enhanced screening (where GPs were paid for setting up record searches (£500), provided with a ‘prompt to screen’ notification on eligible

patients' electronic records, reimbursed £25 for each patient who signed a consent form, and supported by a dedicated clinician). We previously completed qualitative studies examining attitudes to viral hepatitis in migrants¹³ and we used these data to develop an enhanced invitation letter (Supplementary information S1), validated in focus group sessions. Embedded within the trial was an assessment of the impact of this letter on screening when compared to a standard letter, and practices were cluster randomised to send either letter. Patients tested within 31 days of the letter's dispatch were deemed to have responded.

We initially planned to test all eligible patients in each practice. However, it became clear that there were more eligible patients in each practice than estimated (500) due to practice mergers leading to larger practices with increased patient numbers. To avoid over-recruitment a protocol modification 'capped' the number of patients to 500 at some practices whilst allowing others to recruit all eligible patients so that we could assess the feasibility of rolling out the intervention (See Supplementary Information S2 for sample size calculations). The pre-specified primary aims were a) to determine whether interventional ("enhanced") screening is more cost-effective than control ("standard") screening in the detection of viral hepatitis in immigrant patients in primary care, b) to determine the screening uptake rate of intervention practices compared to controls and c) to determine whether the provision of an enhanced patient information invitation letter increased screening uptake compared to a standard letter. To determine whether screening immigrants in an area of low immigrant density was effective we conducted a parallel sub-study with identical procedures and outcome measures in such an area (Oxfordshire).

To examine engagement with diagnostic and therapeutic procedures we conducted a second, embedded, trial. The pre-specified aim of this trial was to determine whether community based therapy is superior to conventional delivery of treatment (hospital based) as measured by engagement with management.

Participants

Patients were eligible if they were > 18 years old, they or their parents were born in a country with prevalence of viral hepatitis >2% (World Health Organisation - listed in Protocol, Appendix), had no previous documented test for HBV and HCV. In the main study recruitment and testing ran from 31st October 2013 to 4th February 2017 with each practice recruiting over 18 consecutive calendar months. In Oxford, recruitment and testing took place over 18 calendar months between 22nd May 2015 and 16th April 2017. Eligible patients were identified by review of GP electronic records (EMIS or SystmOne) using a bespoke algorithm to identify coded ethnicity, language, country of birth and previous viral hepatitis testing and diagnosis. We did not distinguish first and second generation immigrants.

For practices where the number of patients was 'capped', 500 patients from the eligible population were selected using the random number facility on the electronic records system. These patients formed the eligible cohort, who were contacted for testing. For practices where no cap applied, all identified patients formed the eligible cohort. Patients who were not on the eligible list were tested were excluded. At the end of the intervention period, in control and 'uncapped' practices the eligibility search was repeated and eligible patients who joined the practice during the study (present on final but not initial eligibility lists) were included as 'new registrants'. We

had no data on patients who registered and left the practice within the 18 month study period.

Intervention

All included patients were sent a letter inviting them to attend for viral hepatitis testing and patients were tested following an appointment made after responding or when they attended the practice for other reasons. All eligible patients had an electronic prompt attached to their records visible whenever they attended. Patients provided written consent prior to testing and details were recorded on an electronic form in the GP records. Testing for viral hepatitis was performed when a bespoke request form was sent to the local virology laboratory where standard tests for HBV and HCV were performed. A testing algorithm (Supplementary 3) was deployed with re-tests for indeterminate results. The test result was provided to the GP practice for entry on the patient's records. An anonymised result was provided to the trial researchers to facilitate data checking. Data collection from practices was performed monthly by electronic data capture. After 18 months the intervention ceased.

Randomisation, blinding and sample size

Randomisation was performed as above by the PCTU at QMUL. The analysis team were blinded to the nature of the allocation arm. Patients who tested positive for viral hepatitis were not informed of the arm to which their practice was allocated until after they had consented to enter the embedded trial of community versus standard care.

Embedded trial of community versus standard care

Patients who tested positive for viral hepatitis in the screening trial were eligible for enrolment in a second, embedded, trial comparing standard hospital-based care to community care. Interventional screening practices were cluster randomised to standard or community care. Following a diagnosis of viral hepatitis patients were referred to the local hospital. At this visit patients were asked to consent to participate in a trial of standard or community care by a clinician blinded to practice allocation. Following consent patients were informed of the allocation of their practice and treated in the community at one of nine GP surgeries by a visiting hospital nurse/doctor (community care), or at hospital outpatients (standard care). Community care was delivered at GP surgeries that were not necessarily the surgery where the patient was normally seen. Patients who did not consent to community care or who were tested before community care was established were given standard care.

All patients were asked to complete a fibrosis evaluation (liver biopsy or fibroscan) and were offered NHS treatment. For active HBV infection therapy was interferon or nucleotide-based and for HCV this was interferon-based initially but latterly was with all oral therapy as this became available (initially for patients with genotype 1 and later genotype 3). Given the evolving complexity of management options we adopted pragmatic criteria for engagement based on attendance. Engagement with diagnostic and prognostic assessment was defined as completion of three events (diagnostic assessment, fibrosis assessment with fibroscan and/or ultrasound and clinical management according to local policy). For patients who were HCV antibody positive but HCV RNA negative attending a diagnostic visit on two occasions was deemed 'engaged'. Following engagement patients were asked to adhere to a treatment plan of either monitoring (inactive HBV or mild HCV not prioritised for

therapy) or antiviral therapy. Adherence among monitored patients was defined as attending at least one visit within six months. Patients prescribed medication were deemed adherent if the clinical staff reported <20% of medication was unused at clinic review. A successful outcome was defined as sustained virologic response (SVR) 12 weeks after treatment completion (HCV) or a reduction in viral load to <80% of starting value within 12 weeks (HBV).

Outcomes and statistical analyses

We calculated testing uptake rates on an intention-to-treat basis and used these to derive incidence rate ratios (IRRs) adjusted for site and the number of eligible patients over the 18 month recruitment period for the trial. To determine whether a bespoke invitation letter improved testing we defined tested in response to the invitation letter as ‘testing within 31 days of the letter’s dispatch’ and evaluated IRR. Testing rates were modelled using Poisson regression. The dependent variable was the number of patients tested in each practice, the number of eligible patients was the exposure variable, practice a random effect, and site and number of eligible patients included as covariates. Generalised estimating equations (xtgee command in Stata) using logit link with exchangeable correlation matrix and robust standard errors were used to model engagement rates. Site, number of eligible patients group, age and sex were included as covariates. Model based ICCs were derived. If ICCs were found to be negative, the intervention effects from the analysis not adjusting for clustering are presented. Analysis was carried out using Stata version 14.1. A 5% significance level (two-sided) was used for all significance tests. We also calculated prevalence rates for viral hepatitis.

In the nested trial on treatment engagement among infected patients, we assessed engagement with the diagnostic and prognostic assessment.

For the economic evaluation, the incremental cost per quality-adjusted life year (QALY) of the HepFREE programme, compared with standard practice, was estimated using a modified decision tree /Markov model structure. Patient recruitment, clinical assessment and treatment were modelled using data from this project. Modelling of usual practice was assumed to follow similar procedures, and was based on the number of positive cases reported. These data were used to estimate the year-on-year schedule of presentation for those patients in both arms that were undetected during the programme. In the base case scenario, treatment regimen allocation was on an intention-to-treat-basis, modelling a combination of interferon and all-oral treatment regimes. Clinical outcomes for patients still undergoing treatment at trial end were imputed using published efficacy data. Modelled patients were followed over a lifetime horizon. Long term follow up of HBV cases was based on previous models and annual transition probabilities¹³. Data for HCV follow up was based on meta-regression of disease progression¹⁴. Post-transplant survival was estimated from UK transplantation service 2016 data. Costs of treatment were estimated from British National Formulary and did not include negotiated discounts. Scenarios with a range of discounts were modelled to allow an assessment of likely benefits for different prices. Costs of disease management were calculated from NHS national tariff bundles. Quality of life data was based on Levy (HBV)¹⁵ and Wright (HCV)¹⁶ and discount rates of 3.5% for costs and benefits were applied. Sensitivity of the base case results to parameter variation was extensively tested by one-way

parameter variation and probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. Patient recruitment variability was assessed at the cluster level.

Role of the funding source

This study was funded by a National Institute for Health Research Programme Grant. The funder played no part in the design, conduct or analysis of the study.

Results

Sixty three general practices in three areas of high immigrant density agreed to participate. Five withdrew before contributing data and fifty eight were randomised - 50 to the intervention and eight as controls. Fifteen intervention practices were asked to invite all eligible patients ('uncapped') and 35 were 'capped' to 500 eligible patients. Nine practices in Oxford took part in the parallel observational sub-study. Practice allocation and eligible patient numbers in each arm are detailed in Figure 1. Allocated groups were well matched in terms of practice and population characteristics (Table 1). There were slightly fewer patients from Pakistan amongst newly registered patients and capped practices. In Oxford the population differed from the other sites with fewer people from the Indian sub-continent.

Testing was uncommon in control practices (1.7%) and significantly increased in intervention practices (19.5%, IRR 3.7 (95% CI:1.3 to10.5), $P = 0.014$ – Table 2A). The difference was more marked in patients initially registered with the practice: 20.3% tested in intervention practices compared to 1% in controls (IRR 5.2, 95% CI: 1.9 to14.3, $P = 0.001$) whereas in newly registered patients 4.8% of patients were tested in control practices compared to 12.8% in those exposed to the intervention. Characteristics of untested and tested patients are shown in Table 1 - testing was more common in people >40 years old compared to younger patients and this was noted in both initially registered and newly registered patients (28% vs 14.9% and 24.6% vs 11.4% respectively). Testing was most common in people whose origins were in the Indian sub-continent, in particular Pakistan. Nearly 60% of those tested were from Pakistan whilst only 32.5% of those eligible for testing were of this ethnicity. Overall 36% of eligible patients from Pakistan were screened. People of Chinese or African origin were rarely tested. Testing in response to a letter from the practice showed that an enhanced invitation letter did not increase attendance (standard letter testing rates were 4.5% vs 3.7% with the enhanced letter, IRR = 0.7, 95% CI: 0.38 to 1.3, $P = 0.26$, Table 2B). Screening rates within 31 days of dispatch of the letter were reduced (4%) compared to testing outside this window. In the 9 practices from an area of low immigrant density, 515 of 6854 (7.5%) eligible patients were tested and a similar trend was observed with older patients from the Indian sub-continent being most likely to attend.

Table 3 shows the characteristics of the 2% of patients testing positive. In the 1% of patients who had antibodies against HCV only 0.3% were viraemic. We noted an increase in positive tests in patients screened in control practices (17 of 543, 3.1%) compared to 220 of 11386 (1.9%) in intervention practices and a similar increase was noted in newly registered patients - 29 of 1134 (2.6%) compared to registered patients 271 of 10,795 (1.9%). In an area of low immigrant density 1.3% of patients were infected and all had HBV.

A total of 220 people with chronic viral hepatitis (HBsAg or HCV antibodies detected in serum) were identified and were eligible to enrol in the second, embedded, trial to assess engagement and adherence. The CONSORT diagram and patient characteristics are described in Supplementary information which shows that the groups were well matched. The majority of infected patients (129) were allocated to 'community care', 91 to 'standard care'. There was no significant difference in engagement with the diagnostic and prognostic assessment between the two groups (80 of 91 (87.9%) patients in standard care engaged compared to 105 of 129 (81.4%) in community care – IRR 0.76, 95% CI: 0.23 to 2.53, $P = 0.65$) by strict ITT analysis.

The patient cohort was heterogeneous and not all required therapy. Of the 220 patients, 61 were HCV RNA negative and 18 were not eligible for further intervention (already engaged at another hospital (9), cleared virus between reflex viral testing and confirmatory testing (3) or declined further participation (6)) leaving 141 infected patients. Some patients were not immediately able to access community therapy and defaulted to standard, hospital, care and of the 66 patients eligible for therapy 51 consented to participate in the second trial of community engagement, 33 in practices randomised to community care and 18 in practices randomised to standard care. Of the 33 patients in the community care arm, 30 (90.9%) attended at least one follow-up appointment within 6 months. 8 were HCV RNA positive, 6 of whom were treated and achieved SVR12, 1 was treated with DAAs and had not reached 12 weeks post treatment at study closure, and 1 was awaiting therapy. Twenty HBsAg positive patients were eAg negative and required ongoing monitoring at follow-up, 1 HBsAg positive patient had a high DNA level and was commenced on antiviral therapy, achieving an undetectable VL within 3 months, and 1 HBsAg positive patient was eAg positive with a low viral load requiring observation. Of the 18 randomised to secondary care 16 (88.9%) attended follow-up within 6 months. Four were HCV RNA positive, all of whom awaited DAA therapy, 12 were HBsAg positive, eAg negative and all required monitoring.

Given the small proportion of patients who agreed to enrol into a treatment trial we conducted a per protocol analysis of engagement. Of the 25 HBV infected patients in the community care arm 24 (87.5%) adhered to the management plan. Seventy-one patients were treated in standard, hospital setting (14 in the trial arm allocated to this setting, and 57 by default) and 61 (86%) were adherent. Of the 35 HCV-infected patients 8 in the community care arm and all (100%) were adherent. Twenty-seven patients were treated in standard hospital settings (4 in the trial arm allocated to this setting and 23 received this by default). All (100%) were adherent. In the Oxford parallel study all HBV infected patients identified adhered to therapy.

Of the 97 patients with HBsAg who completed a diagnostic assessment 2 had Delta virus infection, 5 were HBeAg positive and 7 (7%) had severe fibrosis or cirrhosis on liver biopsy. For the 45 patients with chronic HCV infection 40 (88%) had genotype 3 and 5 (11%) had cirrhosis. During the intervention phase one patient developed thyroiditis, no other trial related harms were noted during the study.

In the base case, the intervention was cost-effective at willingness to pay thresholds in excess of £8,540 per QALY. Treatment with pure DAA regimes for HCV made the joint intervention cost-effective at willingness to pay (WTP) thresholds between £6,935 and £18,185 per QALY depending on pricing and the regime/treatment

duration applied. Treatment of over 40s (mean age 50) was cost-effective at WTP thresholds in excess of £15,696. Screening based on ethnic background was cost-effective for Pakistani ethnicity at WTP thresholds in excess of £9,523 per QALY. The intervention was unlikely to be cost-effective for cohorts with mean age greater than 56. Results from the PSA indicated that the intervention is likely to be cost-effective in the vast majority of scenarios, with a mean incremental cost-effectiveness ratio (ICER) of £5,292. This result is lower than the deterministic mean, in part because the probabilistic analysis adjusts for the poor screening performance of some larger GP practices. This issue appears to have predominantly affected practices where HBV was the more prevalent infection.

Discussion

Modelling and small scale studies have indicated that screening migrants for viral hepatitis is likely to be clinically and cost effective¹⁷. Such studies typically involve motivated clinicians and suggest that a large proportion of people will be tested and referred for therapy. A study in the Netherlands estimated that 39-75% of patients would be tested and referred¹⁷. Based on these studies many screening guidelines advocate testing migrants and in 2012 the English National Institute for Health and Care Excellence (NICE) issued guidance recommending testing of migrants for viral hepatitis in primary care settings¹⁸. The impact of these guidelines and the benefits of widespread testing have not been assessed. HepFREE was a large scale national trial to examine screening rates in migrants by primary care practitioners who were either encouraged to screen by providing an educational programme (controls) or incentivised to screen with funding and support. We find that testing for viral hepatitis was much less common than expected - very few people were tested in control practices and supported, incentivised GPs tested 20% of eligible patients, substantially lower than the testing rates used in previous models. People from Pakistan were most likely to be tested, which may reflect the enthusiasm of primary care physicians in the sites with a high prevalence of such patients (chiefly Bradford) but in all sites testing in other ethnicities was poor. Older patients were more likely to attend for testing, perhaps reflecting more contact with primary care. We were surprised to find that a tailored letter was of little value with relatively few patients responding to a letter. This is a costly intervention and we suggest that this approach is not pursued. Engagement following diagnosis was excellent in patients treated in both hospital and community settings, and there is no evidence that expensive, community, care is beneficial, in contrast to other populations at risk of hepatitis, such as injection drug users, where community therapy may be advantageous¹⁹. Given the increase in testing and its cost effectiveness when general practitioners were incentivised to test migrants for viral hepatitis we suggest that this be introduced into future hepatitis elimination programmes. However the limitations of this strategy need to be considered as only a minority of patients attended. We suggest that further interventions, such as a targeted advertising campaign, be considered to increase testing further.

The prevalence of viral hepatitis was approximately 2% and in our study only 30% of patients with HCV antibodies were viraemic, substantially lower than previous reports²⁰. This finding has implications for future hepatitis C elimination programmes - there

may be fewer patients with treatment-requiring HCV than believed. Our previous community based screening studies in the same geographical areas¹⁴ found a higher prevalence of viraemia and it is possible that older viraemic patients have either died, retired to their country of birth or sought treatment, perhaps outside the NHS using generic drugs widely available in Pakistan. Further work will be required in immigrant communities at risk of infection to confirm these observations.

We attempted to conduct a randomised trial of community versus hospital-based care. However setting up treatment in the community proved challenging with complex logistics reducing the availability of easy access, community treatment. When patients were given the option of waiting for an opportunity to undergo treatment close to home or receive immediate care in the hospital they invariably opted for hospital treatment. On a per-protocol analysis it was clear that adherence to hospital based care was excellent and although our trial was technically unsatisfactory due to poor adherence to the protocol it seems likely that for this population community based care is not required.

The cost effectiveness analysis indicates that the intervention is cost effective at current thresholds even when the listed drug price was used. Negotiations by NHSE and other health care payers have led to significant reductions in the price of antivirals for HCV and the expiration of the patents for the common HBV drugs has led to cost reductions. The intervention is therefore highly cost effective in current settings. Interestingly, cost effectiveness was less marked in the elderly – a result driven by a combination of the detection of less aggressive cases, and the reduction of the time horizon needed to recoup the benefits. Joint screening for HBV and HCV coupled with lower than expected test costs meant that the intervention might be cost-effective at disease prevalence as low as 0.3%, however this result also benefitted from a high uptake of treatment and a low proportion of patients lost to follow up. Variation in disease management costs and utility of individual disease states did not significantly influence the result in terms of proximity to recognised WTP thresholds.

In summary we find that interventions to increase GP testing for chronic viral hepatitis in primary care settings are clinically and cost effective. Given the WHO's challenging goal to reduce the burden of these infections screening immigrant populations for these infections is likely to form an important part of campaigns to reduce the disease burden. However the finding that only 20% of patients attended for screening even with the interventions in this trial indicates that further measures will be required to eliminate viral hepatitis as a health care concern.

Declaration of interests

Professors Foster and Agarwal have received speaker and consultancy fees from companies that market drugs for the treatment of viral hepatitis, specifically AbbVie, Gilead and Merck.

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We are grateful to Jessica Gavirez who helped set up and manage the study and to our GP colleagues who worked tirelessly to complete this work.

Legends to Figures

Figure 1

CONSORT diagram of the main HepFREE trial.

General practices from areas of high immigrant density (Bradford, NE and SE London) were randomised to act as controls or take part in interventional screening. Interventional screening practices were randomised to either standard or community care and a standard invitation or enhanced invitation letter, giving four possible allocations, as shown. In a parallel study in Oxford practices were asked to undertake interventional screening with standard care. Some practices (capped practices) had a limit on the number of patients who could be enrolled (N=500) and others attempted to test all patients. Patients registered with the practice (shown in standard text) as well as newly registered patients (shown *in brackets in italics labelled +xxx*) were offered screening and numbers screened are indicated. Patients who tested positive were eligible to enroll in a second trial to assess the value of community based treatment compared to hospital care.

Table 1

Demographics, gender, ethnicity (recorded by the general practice) and age is shown for the eligible population as well as those screened. Percentages are the percent of the total relevant population.

Table 2

Primary end-points of the HepFREE study.

2A shows IRRs for interventional vs standard screening and 2B shows screening rates in response to an invitation letter.

Table 3

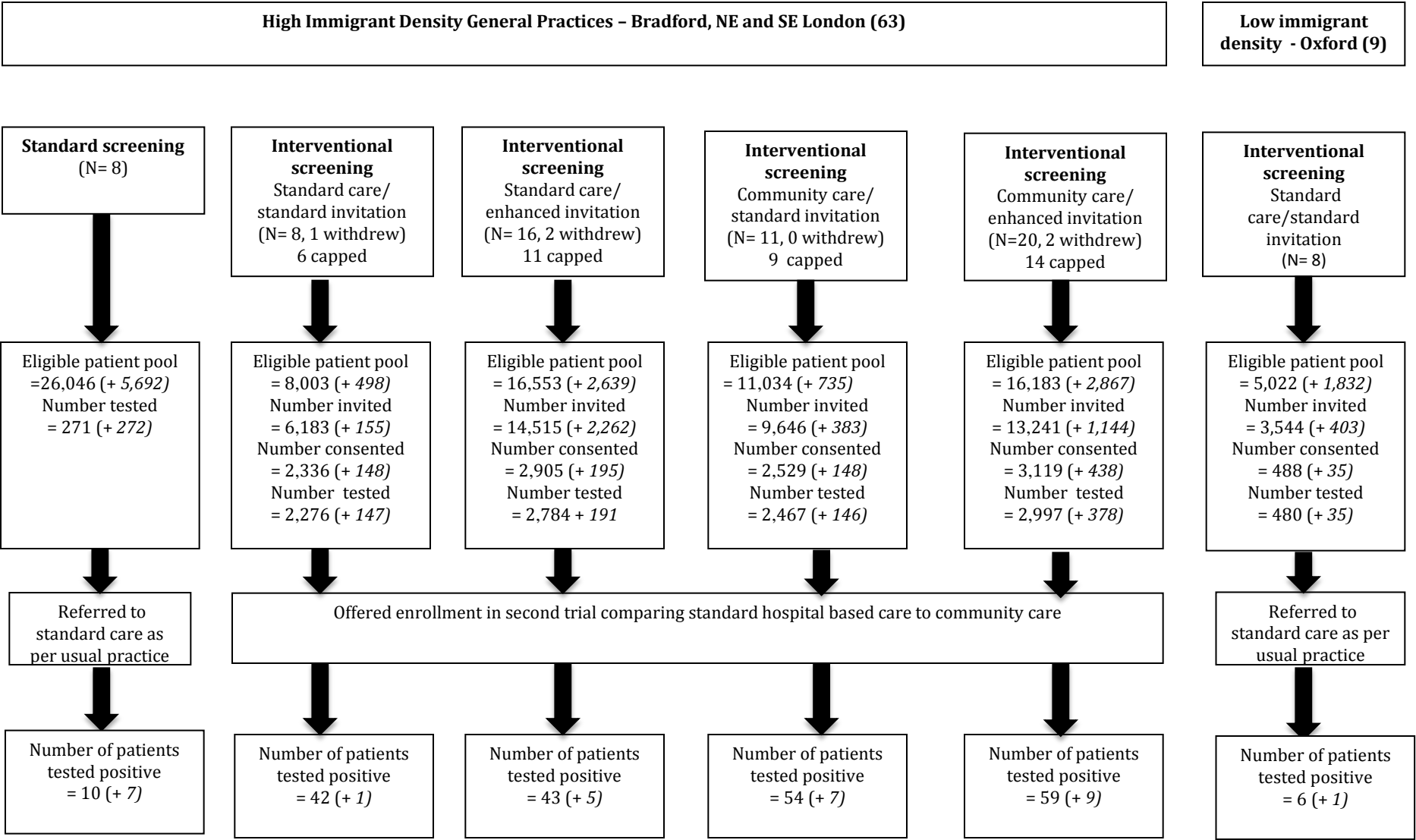
Proportion of patients testing positive for HBV (HBsAg positive) or HCV (antibody and RNA detected by PCR testing).

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Figure



Table

	Control						Intervention High Immigrant Density														Oxford	
	Total		Registered		New registrants		Total		Standard letter		Enhanced letter		Registered		New registrants		Capped		Uncapped			
	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen	Eligible	Screen
	31,738	543 (1.7%)	26,046	271 (1.0%)	5,692	272 (4.8%)	58,512	11386 (19.4%)	19,037	4743 (24.9%)	32,736	5781 (17.6%)	51,773	10524 (20.3%)	6,739	862 (12.8%)	16,970	3173 (18.7%)	41,542	8213 (19.8%)	6,854	515 (7.5%)
Female	16,549 (52.1%)	304 (56.0%)	13,351 (51.3%)	142 (52.4%)	3,198 (56.2%)	162 (59.6%)	30,187 (51.6%)	6,537 (57.4%)	9,524 (50.0%)	2,632 (55.5%)	17,024 (52.0%)	3,427 (59.3%)	26,548 (51.3%)	6,059 (57.6%)	3,639 (54.0%)	478 (55.5%)	8,608 (50.7%)	1,870 (58.9%)	21,579 (51.9%)	4,667 (56.8%)	3,786 (55.2%)	316 (61.4%)
Ethnicity																						
Black	3,142 (9.9%)	112 (20.6%)	2,619 (10.1%)	67 (24.7%)	523 (9.2%)	45 (16.5%)	6,866 (11.7%)	545 (4.8%)	2,727 (14.3%)	209 (4.4%)	3,723 (11.4%)	328 (5.7%)	6,450 (12.5%)	537 (5.1%)	416 (6.2%)	8 (0.9%)	3,419 (20.1%)	372 (11.7%)	3,447 (8.3%)	173 (2.1%)	580 (8.5%)	48 (9.3%)
Bang.	3,289 (10.4%)	61 (11.2%)	2,837 (10.9%)	47 (17.3%)	452 (7.9%)	14 (5.1%)	3,357 (5.7%)	905 (8.0%)	1,480 (7.8%)	412 (8.7%)	1,668 (5.1%)	409 (7.1%)	3,148 (6.1%)	821 (7.8%)	209 (3.1%)	84 (9.7%)	1,835 (10.8%)	363 (11.4%)	1,522 (3.7%)	542 (6.6%)	110 (1.6%)	11 (2.1%)
Indian	4,269 (13.5%)	25 (4.6%)	3,506 (13.5%)	13 (4.8%)	763 (13.4%)	12 (4.4%)	5,499 (9.4%)	1,148 (10.1%)	957 (5.0%)	254 (5.4%)	3,986 (12.2%)	770 (13.3%)	4,943 (9.5%)	1,024 (9.7%)	556 (8.3%)	124 (14.4%)	1,382 (8.1%)	306 (9.6%)	4,117 (9.9%)	842 (10.3%)	653 (9.5%)	54 (10.5%)
Pak.	8,771 (27.6%)	38 (7.0%)	7,874 (30.2%)	24 (8.9%)	897 (15.8%)	14 (5.1%)	19,001 (32.5%)	6,814 (59.9%)	7,215 (37.9%)	3,224 (68.0%)	10,482 (32.0%)	3,190 (55.2%)	17,697 (34.2%)	6,414 (61.0%)	1,304 (19.4%)	400 (46.4%)	3,920 (23.1%)	1,352 (42.6%)	15,081 (36.3%)	5,462 (66.5%)	313 (4.6%)	20 (3.9%)
Other	2,857 (9.0%)	55 (10.1%)	2,376 (9.1%)	28 (10.3%)	481 (8.5%)	27 (9.9%)	4,790 (8.2%)	350 (3.1%)	1,011 (5.3%)	93 (2.0%)	2,898 (8.9%)	231 (4.0%)	3,909 (7.6%)	324 (3.1%)	881 (13.1%)	26 (3.0%)	1,264 (7.4%)	139 (4.4%)	3,526 (8.5%)	211 (2.6%)	1,027 (15.0%)	105 (20.4%)
Asian	1,309 (4.1%)	9 (1.7%)	965 (3.7%)	1 (0.4%)	344 (6.0%)	8 (2.9%)	3,126 (5.3%)	406 (3.6%)	501 (2.6%)	87 (1.8%)	1,930 (5.9%)	219 (3.8%)	2,431 (4.7%)	306 (2.9%)	695 (10.3%)	100 (11.6%)	642 (3.8%)	72 (2.3%)	2,484 (6.0%)	334 (4.1%)	674 (9.8%)	43 (8.3%)
Cauc.	8,101 (25.5%)	243 (44.8%)	5,869 (22.5%)	91 (33.6%)	2,232 (39.2%)	152 (55.9%)	15,873 (27.1%)	1,218 (10.7%)	5,146 (27.0%)	464 (9.8%)	8,049 (24.6%)	634 (11.0%)	13,195 (25.5%)	1,098 (10.4%)	2,678 (39.7%)	120 (13.9%)	4,508 (26.6%)	569 (17.9%)	11,365 (27.4%)	649 (7.9%)	3,497 (51.0%)	234 (45.4%)
Age																						
18-19	882 (2.8%)	6 (1.1%)	882 (3.4%)	6 (2.2%)	0 (0.0%)	0 (0.0%)	1,619 (2.8%)	223 (2.0%)	686 (3.6%)	122 (2.6%)	933 (2.9%)	101 (1.7%)	1,619 (3.1%)	223 (2.1%)	0 (0.0%)	0 (0.0%)	352 (2.1%)	27 (0.9%)	1,267 (3.0%)	196 (2.4%)	110 (1.6%)	2 (0.4%)
20-29	9,523 (30.0%)	180 (33.1%)	7,107 (27.3%)	56 (20.7%)	2,416 (42.4%)	124 (45.6%)	16,816 (28.7%)	2,029 (17.8%)	4,864 (25.6%)	823 (17.4%)	9,068 (27.7%)	942 (16.3%)	13,932 (26.9%)	1,765 (16.8%)	2,884 (42.8%)	264 (30.6%)	4,374 (25.8%)	448 (14.1%)	12,442 (30.0%)	1,581 (19.2%)	1,649 (24.1%)	49 (9.5%)
30-39	10,023 (31.6%)	185 (34.1%)	8,035 (30.8%)	94 (34.7%)	1,988 (34.9%)	91 (33.5%)	17,680 (30.2%)	2,899 (25.5%)	5,391 (28.3%)	1,268 (26.7%)	9,991 (30.5%)	1,363 (23.6%)	15,382 (29.7%)	2,631 (25.0%)	2,298 (34.1%)	268 (31.1%)	4,922 (29.0%)	746 (23.5%)	12,758 (30.7%)	2,153 (26.2%)	2,532 (36.9%)	167 (32.4%)
40-49	5,413 (17.1%)	113 (20.8%)	4,681 (18.0%)	66 (24.4%)	732 (12.9%)	47 (17.3%)	10,457 (17.9%)	2,606 (22.9%)	3,640 (19.1%)	1,054 (22.2%)	5,974 (18.2%)	1,397 (24.2%)	9,614 (18.6%)	2,451 (23.3%)	843 (12.5%)	155 (18.0%)	3,393 (20.0%)	754 (23.8%)	7,064 (17.0%)	1,852 (22.5%)	1,344 (19.6%)	134 (26.0%)
50-59	2,846 (9.0%)	38 (7.0%)	2,550 (9.8%)	30 (11.1%)	296 (5.2%)	8 (2.9%)	5,967 (10.2%)	1,703 (15.0%)	2,196 (11.5%)	682 (14.4%)	3,365 (10.3%)	924 (16.0%)	5,561 (10.7%)	1,606 (15.3%)	406 (6.0%)	97 (11.3%)	1,992 (11.7%)	545 (17.2%)	3,975 (9.6%)	1,158 (14.1%)	643 (9.4%)	76 (14.8%)
60-69	1,602 (5.0%)	17 (3.1%)	1,472 (5.7%)	16 (5.9%)	130 (2.3%)	1 (0.4%)	3,133 (5.4%)	1,130 (9.9%)	1,175 (6.2%)	470 (9.9%)	1,766 (5.4%)	612 (10.6%)	2,941 (5.7%)	1,082 (10.3%)	192 (2.8%)	48 (5.6%)	1,030 (6.1%)	389 (12.3%)	2,103 (5.1%)	741 (9.0%)	324 (4.7%)	53 (10.3%)
>70	1,449 (4.6%)	4 (0.7%)	1319 (5.1%)	3 (1.1%)	130 (2.3%)	1 (0.4%)	2,840 (4.9%)	796 (7.0%)	1,085 (5.7%)	324 (6.8%)	1,639 (5.0%)	442 (7.6%)	2,724 (5.3%)	766 (7.3%)	116 (1.7%)	30 (3.5%)	907 (5.3%)	264 (8.3%)	1,933 (4.7%)	532 (6.5%)	252 (3.7%)	34 (6.6%)

Table 2A 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

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

**Intraclass 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 2B: 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 (<i>number of practices = 18</i>)	720 / 15,844	4.5%	0.703 [0.378 to 1.306]	0.265
Enhanced invitation (<i>number of practices = 32</i>)	1,032 / 28,095	3.7%		

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

Table

Total	Total				High Immigrant Density (Bradford, NE, SE london)								Oxford	
					Control			Intervention						
	Number tested	HBsAg	HCV abod +ve	HCV RNA +ve	Number tested	HBsAg +ve	HCV Abod +ve*	Number tested	HBsAg +ve	HCV Abod +ve	HCV RNA +ve	Number tested	HBsAg +ve	
	11,929	127 (1.06%)	111 (0.93%)	36 (0.30%)	543	12 (2.21%)	5 (0.92%)	11,386	115 (1.01%)	106 (0.93%)	36 (0.32%)	515	7 (1.36%)	
Gender														
Female	6,841	41 (0.6%)	63 (0.92%)	20 (0.29%)	304	4 (1.32%)	5 (1.64%)	6,537	37 (0.57%)	58 (0.89%)	20 (0.31%)	316	2 (0.63%)	
Male	5,087	86 (1.69%)	48 (0.94%)	16 (0.31%)	239	8 (3.35%)	0	4,848	78 (1.68%)	48 (0.99%)	16 (0.33%)	199	5 (2.51%)	
Ethnicity														
Black	657	9 (1.37%)	2 (0.3%)	0	112	2 (1.79%)	1 (0.89%)	545	7 (1.28%)	1 (0.18%)	0	48	1 (2.08%)	
Bangladesh	966	10 (1.04%)	3 (0.31%)	0	61	2 (3.28%)	0	905	8 (0.88%)	3 (0.33%)	0	11	0	
Indian	1,173	7 (0.60%)	4 (0.34%)	2 (0.17%)	25	0	0	1,148	7 (0.71%)	4 (0.35%)	2 (0.17%)	54	1 (1.85%)	
Pakistan	6,852	53 (0.77%)	89 (1.3%)	32 (0.47%)	38	2 (5.26%)	2 (5.26%)	6,814	51 (0.75%)	87 (1.28%)	32 (0.47%)	20	0	
Other Asian	405	11 (2.72%)	1 (0.25%)	0	55	1 (1.82%)	1 (1.82%)	350	10 (2.86%)	0	0	105	2 (1.90%)	
Eastern Cauc.	415	8 (1.93%)	4 (0.96%)	2 (0.48%)	9	1 (11.11%)	0	406	7 (1.72%)	4 (0.99%)	2 (0.49%)	43	1 (2.33%)	
Other	1,461	29 (1.98%)	8 (0.55%)	0	243	4 (1.65%)	1 (0.41%)	1,218	25 (2.05%)	7 (0.57%)	0	234	2 (0.85%)	
Age														
18-19	229	0	0	0	6	0	0	223	0	0	0	2	0	
20-29	2,209	18	8 (0.36%)	5 (0.23%)	180	3 (1.67%)	1 (0.56%)	2,029	15 (0.74%)	7 (0.34%)	5 (0.25%)	49	1 (2.04%)	
30-39	3,084	34 (1.10%)	35 (1.13%)	16 (0.52%)	185	8 (4.32%)	1 (0.54%)	2,899	26 (0.90%)	34 (1.17%)	16 (0.55%)	167	0	
40-49	2,719	32 (1.18%)	34	7 (0.26%)	113	0	2 (1.77%)	2,606	32 (1.23%)	32 (1.23%)	7 (0.27%)	134	3 (2.24%)	
50-59	1,741	20 (1.15%)	19 (1.09%)	5 (0.29%)	38	1 (2.63%)	1 (2.63%)	1,703	19 (1.12%)	18 (1.06%)	5 (0.29%)	76	1 (1.32%)	
60-69	1,147	17 (1.48%)	8 (0.70%)	1 (0.09%)	17	0	0	1,130	17 (1.50%)	8 (0.71%)	1 (0.09%)	53	2 (3.77%)	
>70	800	6 (0.75%)	7 (0.88%)	2 (0.25%)	4	0	0	796	6 (0.75%)	7 (0.88%)	2 (0.25%)	34	0	

* all patients were HCV RNA undetected

Supplementary Material

[Click here to download Supplementary Material: HepFREE Supplementary Information Submitted.pdf](#)

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

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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 18 th 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	<p><u>Primary objectives</u></p> <ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• 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 be 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'.

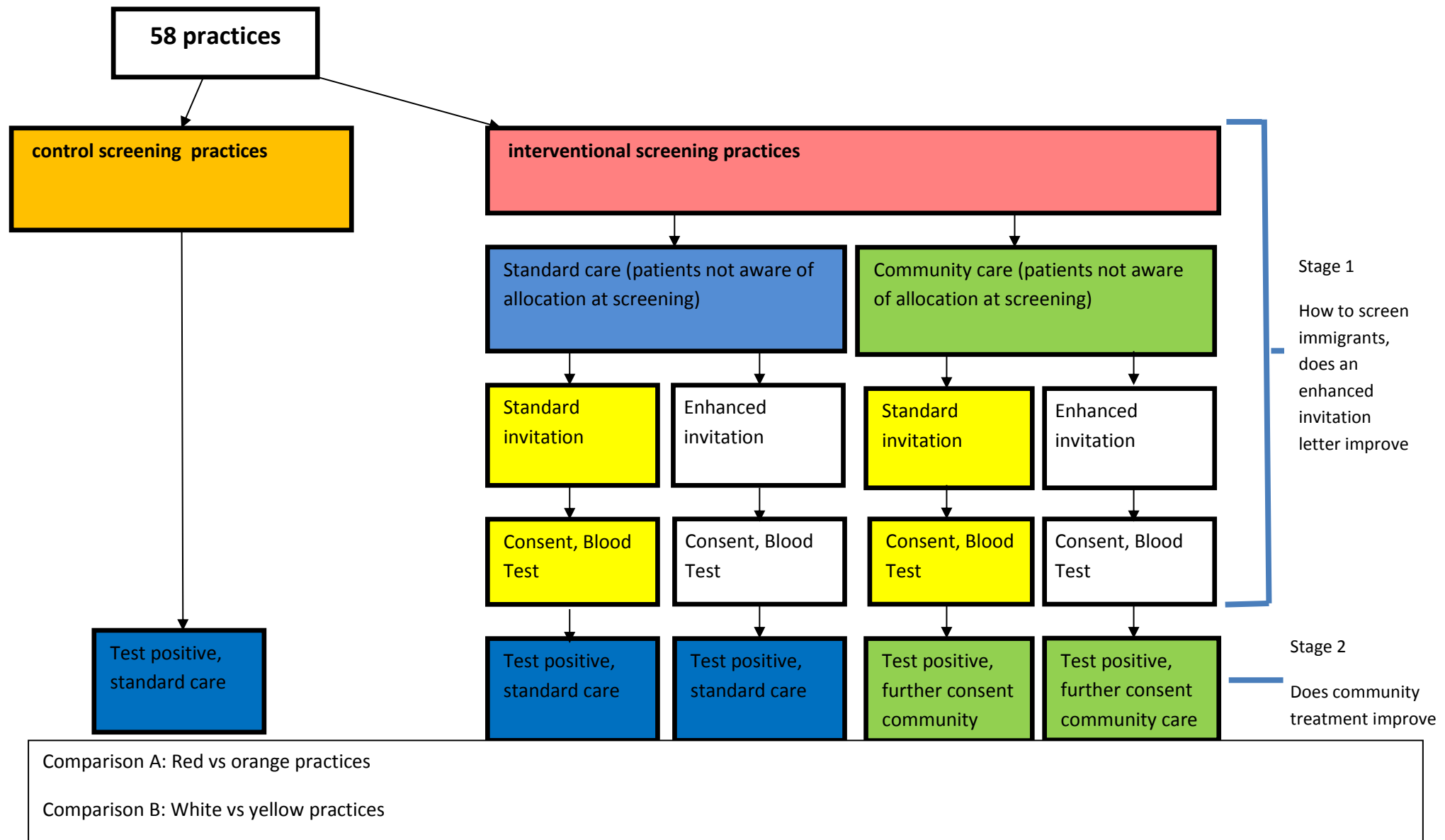
2.2 Trial Design

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 change 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 or 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 fast developments in treatment availabilities for hepatitis C and change in NHS policy, with regards to prescribing new hepatitis therapies, the 'clinical management plan' for some patients may change

throughout the course of the trial. Continuing to collect outcome data for all HepFree patients that screen positive until Feb 2017 will enable us to obtain 'adherence to therapy' and 'response to therapy' (secondary outcomes) information for patients whose treatment options change during the trial period.

For patients who are randomised to community care, they will continue to receive their hepatology care, if appropriate, in the community until the HepFree data collection stops in February 2017. This is to allow the patients enough time to adjust to their treatment regimes in the community before moving their care back to 'standard of care' based at the local hospital once their study visits have been completed.

Adherence to therapy will be analysed as a secondary study outcome. Adherence to therapy will be defined as having taken 80% or more of the prescribed medication as described in section 2.1.

In 'community care' practices, patients who agree to undergo therapy in the community will be asked to attend a designated GP practice where a specialist viral hepatitis nurse and/or hepatologist will attend and deliver care in the community in accordance with a community treatment algorithm established and supervised by the local secondary care centre (see section 4.4).

4.2.5 Investigating Barriers to Screening in Primary Care. "The HepFree Provider Experience" Qualitative Research

This is a qualitative substudy linked to the screening rates in Stage 1 of the HepFree trial. Data collected so far from stage 1 of the HepFree study shows that screening rates differ vastly across different GP practices (from 2%-90%) and the purpose of this substudy is to determine why some GP practices are effective at engaging with patients, and others are not. This will enable the HepFree team to make future recommendations about key GP practice characteristics that indicate the hepatitis B/C screening intervention would be most effective.

This substudy follows on from previous pre-trial research into the attitudes of primary care healthcare workers towards screening patients for viral hepatitis. (Study approved through the Queen Mary Research Ethics Committee - Ref no: QMREC2012/02). Healthcare workers of various grades were interviewed at 14 GP practices in Bradford, East London and South London between July-October 2014. Since then, all 14 GP practices have participated in the 18 months of "HepFree" viral hepatitis screening programme.

In this qualitative substudy we will interview a general practitioner, practice nurse, healthcare administrator and/or practice manager at 12-14 practices to assess their attitudes to screening in primary care following completion of the screening programme. All interviewees are adult healthcare workers, and many of them will also have contributed to the pre-trial qualitative research. Written informed consent will be sought from GP practice staff who agree to be interviewed. A participant information sheet will be provided detailing the aims of the interviews. All interviewees will be made aware that participation is voluntary and they can stop the interview, or refuse to answer questions, at any time. If the interviewee was part of the pre-trial research then they will be asked for permission to link information provided as part of this interview with information provided prior to the HepFree trial commencing. Interviewees can opt out of this link if they so wish. Participation in the interviews will be kept confidential. The interviewer will not have access to

identifiable research material from the pre-trial interviews until the interviewees provide elicited 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 conducted 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 questions 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 obtain 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 or significant disability or incapacity
- e) Consists of a congenital abnormality or 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 Prescott 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.
<u>Progress Reports</u>	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
<u>Declaration of the conclusion or early termination of the study</u>	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

		<i>The end of study should be defined in the protocol</i>		
<u>Summary of final Report</u>	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
- Turks 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

1.1 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 _correspondence)
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: <ul style="list-style-type: none"> - 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

1.2 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	
1 st 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.
2 nd 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
3 rd 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.

