1. Title: A comprehensive model and economic evaluation of HCV elimination amongst people who inject drugs in England to guide testing and treatment intervention policy and implementation

2. Scientific abstract

Hepatitis C (HCV) is a chronic infection with high burden in the UK that is primarily transmitted through injecting drug use. New direct acting antiviral treatments have dramatically increased cure rates, with NHS-England aiming to eliminate HCV as a public health threat ahead of the World Health Organization global elimination goal of 2030. To do this, it has recently announced it will bulk purchase direct acting antivirals, in contracts with pharmaceutical companies worth £1.0 billion. HCV case-finding, linkage to care and treatment, especially among **People Who Inject Drugs (PWID)** will be critical for ensuring these resources are used effectively. There are many potential interventions and alternative HCV care-pathways but there is little understanding on the most cost-effective strategies. This project will provide evidence-based guidance on optimal strategies to eliminate HCV in England.

AIM 1: Review and synthesise data on the costs and effects of HCV case-finding, linkage to care and treatment interventions for PWID
We will update existing systematic reviews of case-finding, linkage to care and treatment interventions among PWID using PRISMA guidelines, including searches of published/grey literature and contacting key authors/stakeholders. We will focus on UK relevant interventions with a comparison group. Cost and outcome data will be extracted from studies. When cost data is unavailable, it will be estimated through requesting information on the intervention's care pathway and resource use data. When data from multiple similar interventions are available, outcome estimates will be synthesised using meta-analysis techniques, otherwise best practise interventions will be selected based on methodological quality and UK relevance.

AIM 2: Determine the most cost-effective case-finding and treatment strategies for achieving HCV elimination among PWID
A dynamic model of HCV transmission will be used to project the impact of existing prevention, case-finding and treatment services in 4 England regions (defined by NHS-England Operational Delivery Networks responsible for delivering HCV treatment). Detailed data will be used to calibrate the model to each region. The model will evaluate the cost-effectiveness of different scenarios of either scaling up existing case-finding and treatment strategies and/or initiating alternative strategies, using results from AIM 1. Intervention scenarios will be compared to determine the most cost-effective strategy for different budget levels and least costly strategies for achieving the elimination goal. Through undertaking sensitivity analyses, we will determine the optimum strategies for other regions.

Timeline: The work will be performed over 3 years with the evidence synthesis occurring in year 1, detailed modelling for 4 England regions in years 1/2, and generalising modelling to other regions in years 2/3.

Impact and Dissemination: The project will help NHS-England maximise the impact achieved from an estimated £1.0 billion investment in achieving HCV elimination. Through partnering with regional and national stakeholders (providers, commissioners, public health agencies, patient representatives), we will ensure the relevance and influence of our modelling in their decision-making. Results will be published in peer review journals and shared at key national and regional stakeholder committees and meetings concerned with decision-making and recommending strategies for elimination.

3. Background and Rationale

Hepatitis C Virus (HCV) infection causes substantial morbidity. In England, 160,000 people are HCV-infected with most (90%) new HCV infections (5000 per year) being due to injecting drug use(1, 2). HCV is estimated to result in annual UK-costs of £280-470 million(3).

Primary prevention interventions for reducing HCV acquisition among PWID are opioid substitution therapy (OST) and needle and syringe programmes (NSP)(4). A recent Cochrane Systematic Review[60] suggests that an individual's risk of HCV acquisition is reduced by 50% (95%CI 37-60%) if they are currently on OST, 56% (95%CI 20-76%) if they currently have high NSP coverage, and 74% (95%CI 11-93%) if they are on both. However, although recent modelling suggests these

interventions have reduced HCV transmission in the UK[64], other modelling evidence suggests they cannot reduce the HCV-burden to low levels(5). The prevention landscape for HCV was transformed with the arrival of highly effective direct-acting antiviral HCV therapies. Existing modelling(6) and emerging empirical data suggest the scale-up of these therapies could have a large prevention benefit(7, 8).

The World Health Organization (WHO) recently developed a HCV elimination strategy(9), setting intervention targets for decreasing HCV incidence by 80% and HCV-related mortality by 65% by 2030. Many countries have initiated HCV elimination programmes, with NHS-England aiming to achieve the WHO goals by 2025(10). The main challenge is how to efficiently scale up treatment to reach these targets, which for England means targeting PWID.

High initial costs for new HCV therapies (£10-20,000 per course) resulted in NHS England limiting the yearly number of treatments (10-15,000) over 2016-2018(11), equating to an annual investment of ~£100 million(12). By April 2018, 24,592 individuals received direct-acting antiviral HCV therapies(11). Although treatment was initially restricted to patients with liver disease(11), reductions in drug costs and diminishing numbers of people linked to care has recently expanded treatment to individuals with mild disease (from 18 to 70% of yearly treatments over 2015-18) or current PWID (from 9 to 27%)(11).

The expansion of treatment among PWID requires improvements in HCV case-finding, linkage to care and treatment interventions since only half of HCV-infected PWID are diagnosed(13) and only 15% of these PWID have been treated(13). This is due to sub-optimum testing (10-38% of new attendees(2)) and linkage to treatment (~10%)(14) in the main settings where PWID are reached (prison and drug services). Many interventions are being piloted to improve case-finding and linkage to treatment among PWID, but there is a lack of understanding on which are needed to effectively scale-up treatment.

Decision-making on HCV treatment strategies in NHS-England occurs through **Operational Delivery Networks (ODN)**(15), which currently receive incentives for meeting annual treatment quotas(15). However, most HCV testing among PWID is undertaken by non-NHS-England organisations (e.g. drug services) in community settings, with patchy coverage and poor linkage to treatment(14). To help meet treatment quotas, many ODN have started investing in community-based case-finding strategies (see review of evidence section). Going forward, NHS-England has recently negotiated an HCV elimination tender with industry (April 2019), investing £1 billion over the next 3-5 years to enable ~100,000 individuals to be treated through removing treatment restrictions and contracting industry to invest in case-finding strategies(10, 16). Approximately 90% of these infected individuals are estimated to be among people that are either active injectors or people who have previously injected drugs[83], emphasising the importance of expanding HCV case-finding and treatment interventions among PWID for enabling this scale-up in treatment and successfully reaching the NHS-England targets for eliminating HCV. To enable and optimise the ongoing investment in HCV treatment among PWID, there is an urgent need to guide strategies for scaling-up case-finding and treatment in this group; without which it may not be possible to identify 100,000 individuals to treat.

Unrestricted access to HCV treatment is quickly becoming a reality. The rate limiting step for achieving HCV elimination is now the scale-up of case-finding and treatment linkage interventions to achieve high treatment coverage, with optimisation of prevention interventions for minimising re-infection. In collaboration with key stake-holders, this project will use economic modelling to determine what package of interventions should be scaled up to efficiently eliminate HCV among PWID in England.

Why is the research needed now?

The research deals with a high priority health problem facing NHS-England - how to eliminate HCV. Although we have the treatment tools to achieve this, there is no guidance on how to efficiently scale up case-finding and treatment interventions in an acceptable and feasible manner. Economic modelling is needed to guide decision-makers on what they should do. This will enable them to dramatically reduce the health and economic burden of HCV in an efficient manner.

Review of evidence

Two recently published systematic reviews identified interventions for improving testing and treatment among PWID(17, 18), including interventions in pharmacies(19), drug treatment services (20-22), prisons (20, 21), and Accident and emergency (A&E)(23) in the UK and Ireland. However, a more

recent evidence review undertaken by **Public Health England (PHE**, led by co-applicant Sema Mandal) (24) suggests these other reviews did not capture numerous case-finding strategies being piloted in the UK. This systematic review focussed on interventions to improve case finding, linkage to treatment, and treatment completion for groups at increased risk for HCV infection. They focussed on studies with a comparison group from the UK, Western Europe, Australia and North America. Searches were conducted in Embase and Medline in March 2019, and a call was put out for relevant projects through research networks and regional Viral Hepatitis leads of Public Health England. This review identified additional UK studies considering case-finding in drug treatment services(25), prison(26-30), pharmacies(31, 32), NSP(33), A&E (34-37), and homeless settings(26, 38), although not all these studies included a comparison group. These interventions use nurses or peers to aid linkage-to-care(25, 26, 38), sometimes with community based treatment(19, 33), while point of care tests(39) are sometimes used to improve retention. Further to this, another on-going systematic review being undertaken by the World Health Organisation on 'Integration, Decentralisation and Task-shifting in Hepatitis C testing and treatment', highlights that there any many more studies that have not yet been published in journals, with their review identifying 61 relevant studies from high income countries published as abstracts (poster and oral presentations) in the 2018 International Hepatitis in Substance Users conference. All identified UK and Irish studies are summarised in Table 1, whether including a comparison group or not.

Table 1: Current interventions to improve HCV cascade of care for PWID in **UK and Ireland**

Setting	**Interventions undertaken**	**Locations and total number of studies**	**Number studies with Comparison group**	**Number studies with cost data**	**Reference or lead investigator if unpublished**
Specialist Drug Treatment Centres	Nurse led testing and linkage to treatment at secondary care or onsite	Multi-site UK, 3 studies	2 (25, 40)	2† (25, 41)	(25, 40, 41)
Pharmacy	Pharmacist led testing and onsite treatment for PWID receiving opioid substitution therapy	Multi-site Scotland, 3 studies	2 (19, 31, 42, 43)	2† (19, 42, 43)	(19, 31, 42, 43)
	Pharmacist led testing and referral to treatment at hospital for PWID getting needle and syringe provision at pharmacy	London, 1 study	0	0	(44)
Needle and syringe programme	Nurse led testing and treatment onsite	Dundee, 1 study	0	1†	(33)
Homeless settings	Mobile van outreach testing with community treatment or referral to treatment at secondary care with peer support	London and Brighton, 3 studies	1 (38)	1*	(26, 38) Geoff Dusheiko, Royal Free Hospital
Prison	Nurse led opt out testing of all new recruits or mass screening with treatment onsite	NE England, Dublin, Dundee and Midlands, 6 studies	2 (28-30)	3‡ (45)	(27-30) Zameer Mohamed, Imperial College; John Dillon Dundee
General Practise	Nurse led testing or risk flagging with treatment in secondary care	Multisite, 2 studies	1	2†	(26, 46)
Accident and emergency	Opt out testing for everyone having routine blood test with treatment at secondary care	London, Dublin and Leeds, 6 studies	2 (36, 37)	1†	(23, 34-37, 47, 48)

*Costing and cost-effectiveness done by us and submitted for publication
†Costing and cost-effectiveness currently being done by us
‡Existing and ongoing costing and cost-effectiveness analyses done by us and others

Overall, current evidence suggests nurse-led coordination of dried blood spot testing provision in drug treatment services increases testing uptake (20, 25), with multidisciplinary or nurse-led care coordination increasing linkage to treatment(21, 25). Onsite HCV treatment in drug treatment services has been shown to be feasible for patients receiving opioid substitution therapy (49-52), but so far, little data has come from UK settings (40) and all studies have lacked comparison to offsite treatment for the same patient group. Findings from pharmacy testing and treatment interventions for PWID suggest that testing and treatment can occur in these settings for PWID on opioid substitution therapy (19, 31, 42, 43), but data were from preliminary studies. Full findings should be available in the next year. Some data also shows testing and treatment is possible in fixed site needle and syringe programmes (53, 54). Research in prisons was limited, and emphasised implementation issues in most sites. In the UK, use of dried blood spot testing (20) and/or opt-out testing evaluations (28, 30) showed increases in testing rates, but testing remained low overall. There was little data on undertaking treatment in prison (29). Homeless outreach or hostel based interventions are taking place(55), but only one study met inclusion criteria of having a comparator; showing that peer support increased linkage to care following HCV diagnosis(38).

These evidence reviews illustrate the wealth of studies that could feed in to our project and the considerable work already being done to synthesis evidence on case finding interventions for PWID. However, they also highlight the need to incorporate conference abstracts in our evidence synthesis to help identify studies that are not yet published. Our project will build on existing systematic reviews, particularly the review undertaken by Public Health England and Bajis et al.[17], to synthesise data for our modelling.

Three systematic reviews (2015, 2016 and 2017) identified economic evaluations of HCV testing approaches for PWID(56-58), mainly including interventions to increase case-finding in GP settings, drug services and prisons. Numerous additional UK studies are emerging that include economic evaluations across varied testing settings (see Table 1), comparing new strategies with standard of care. Many of these analyses are being undertaken by our team as summarised in Table 2, which emphasises the wide range of settings where we will have primary cost data to feed into our modelling.

Our costings are undertaken from a UK National Health Service and Personal and Social Services perspective, with all costs converted to 2018 UK Pounds. Financial and economic costs for each intervention are collected from a provider perspective and classified as capital or recurrent. Data are gathered from each intervention's financial records, salary grades and through staff interviews to determine resource use and spending on: capital buildings, vehicles, training and equipment costs, recurrent staff, supplies, and training costs. Overheads are estimated by interview with intervention staff and their line managers to estimate resource use (staff and buildings/equipment) associated with setting up and running a new intervention. Costs are allocated to designated 'activities' for each intervention: management and administration, research, and intervention activities, depending on the activities of each intervention. This could include outreach sessions, undertaking specific tests, follow-up of diagnosed clients, and peer-support for different visits. Where data exists, a bottom-up ingredients approach is also used to estimate costs for each person coming through the intervention, based on recorded resource use including staff time (nurses, peer or key workers, clinician), diagnostic and clinical tests, and other activities. Transport costs are included if it is a part of the intervention, e.g. outreach. Top-down analyses apportion costs associated with administration and management to activities based on measures such as staff time.

Although some evaluations are still ongoing (see Table 2), preliminary results from our analyses suggest that case-finding interventions in drug services, needle and syringe programmes, prison, accident and emergency, or using mobile outreach could be cost-effective (<£10,000 per quality adjusted life year or QALY). This is the case even when we assume the full list price for HCV therapies (likely to overestimate their real cost). However, no existing economic evaluations have compared across interventions or assessed which combined package could efficiently scale up treatment to eliminate HCV. This is a research priority.

Table 2: Summary of case-finding and linkage to treatment interventions that we are evaluating and collecting cost data from

Name	Setting	Location	Description	Aim	Cost data collected
HepCATT	Drug treatment centres	3 sites in England	Nurse-led case-finding and referral to treatment	Increase referral to	Incremental approach including overheads. Top down approach

Name	Setting	Location	Description	Aim	Cost data collected
			in secondary care with peer support	treatment at hospital	to estimate cost per person tested and per person referred.
Eradicate	Needle and syringe provider	Dundee, Scotland	Nurse-led treatment of active injectors at needle and syringe programme. Testing already in place	Treat active injectors	Ingredients based incremental costing of treatment protocol in needle and syringe programme and drug treatment centres.
HepFriend	Mobile unit targeting homeless	London, England	Nurse- and peer-led case-finding with peer support to attend hospital for HCV treatment. Adherence support by peers.	Increase case-finding and treatment	Top down approach used to determine cost per test, cost per person referred, additional cost per person supported through treatment.
Accident and emergency	Hospital	London, England	Opt-out HCV testing for all individuals receiving blood tests for routine care during their A&E visit. Nurse aids referral.	Increase case-finding and referral to treatment	Ingredient based approach for test cost and resources used trying to refer patient. Costs post-referral are not captured because standard of care.
HepLink	GP prescribers of OST	Dublin, Ireland	Nurse-liaison for patients on OST to determine status and facilitate referral to hospital	Increase linkage to hospital for treatment	Ingredients based approach used to determine cost per test and per person referred. Overheads costed using top down approach.
HepCheck	Prison	Dublin, Ireland	Mass HCV screening in prison by GP and nurse team, followed by nurse led treatment in prison after hospital appraisal.	Increase case-finding in prison	Same approach as HepLink
Super-Dot C	Pharmacy delivering OST	Dundee, Scotland	HCV screening and directly observed HCV therapy by pharmacist	Increase testing and treatment	To be collected in 2019
Epitope Prison	Prison	Dundee, Scotland	Opt out HCV screening on entry with prison-based treatment	Increase testing and treatment	To be collected in 2019
Epitope Drug Services	Drug Treatment Centres	Dundee, Scotland	HCV referral and treatment in drug treatment centres	Increase treatment for PWID on drug treatment	To be collected in 2019

OST: Opioid Substitution therapy

4. Project Aims

To provide evidence-based guidance on optimal strategies to eliminate HCV as a public health problem in England. Specific aims are:

AIM 1: Review and synthesise data on the costs and effects of HCV case-finding, linkage to care and treatment interventions for PWID

AIM 2: Determine the most cost-effective case-finding and treatment strategies for achieving HCV elimination among PWID.

5. Research plan / Methods

Design: Systematic review and economic evaluation of alternative case-finding, linkage to care and treatment strategies for PWID, to inform a cost minimisation analysis of which combination of case finding and treatment interventions should be scaled up to efficiently achieve HCV elimination in England. Regional decision-makers and patient representatives will be active co-investigators and

collaborators in our research to ensure that we evaluate options that are practical and acceptable to the local population and commissioning context, so maximising our influence on decision-making.

Methods for AIM 1: Systematic review and evidence synthesis

We will undertake a systematic review of case-finding, linkage to care and treatment interventions among PWID following PRISMA guidelines (59), updating and expanding a review by Public Health England (PHE, see Review of Evidence section) and Bajis et al. The systematic review will be conducted as part of a broader systematic review and meta-analysis led by collaborators in Australia on global interventions to enhance testing, linkage to treatment, and treatment outcomes for hepatitis C infection among all population groups. The protocol for the review will be registered with PROSPERO. We will search published literature conference abstracts; contacting authors for further information where necessary. Studies will be considered eligible for inclusion if they meet the following criteria:

- **Population**: PWID, or population sub-groups and settings that include a high concentration of PWID, including prisons, homeless services, accident and emergency, mobile outreach, drug services and settings providing opioid substitution therapy such as pharmacies.
- **Interventions:** We will include any intervention that aims to: (1) increase the uptake of testing among individuals in a specific setting that serves PWID; (2) improve the proportion of diagnosed PWID that attend a treatment referral visit and initiated on to treatment; or (3) increase the proportion that are retained, adhere and complete HCV treatment or achieve cure. We will have a specific focus on any interventions suggested by our PPI groups in our search.
- **Comparison**: have a comparison group of participants that either do not receive the intervention or are receiving care as usual (including randomised and non-randomised controls, historical and before and after studies).
- **Outcomes**: measure either HCV testing offer and uptake, referral and assessment for HCV treatment, HCV treatment uptake, HCV treatment outcomes (treatment completion and sustained viral response (SVR – effective cure)).

There will be no limitations on languages but only studies from UK, Western Europe, Australia and North America are likely to be relevant for our modelling analyses, although the overall review will be global.

Peer-reviewed literature search. We will search MEDLINE, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and PsycINFO. Systematic reviews identified with potentially relevant sources will be hand-searched for relevant papers/reports.

Data from international organisations. Relevant documents by international agencies on interventions to improve HCV testing, case-finding, linkage to care and treatment among PWID will be obtained through key contacts and searching their web sites. This will include testing and treatment guidelines by the World Health Organisation, European Centre for Disease Control, European Monitoring Centre on Drugs and Drug Addiction, and International Network of Hepatitis in Substance Users (INHSU).

Conference abstracts. Conference abstracts for key conferences such as INHSU and the International Liver Congress will be searched using their web-based search facility, and posters/presentations obtained for any relevant abstract (either from conference website or through contacting the lead author). The utility of this strategy has been shown previously (see Review of Evidence section).

Screening and Extraction: An Endnote library will be created to catalogue papers/reports, with removal of duplicates. Screening will be conducted in Covidence. We will identify native speakers for non-English data sources, and use the Google Translate function if this is unsuccessful. Screening of titles and abstracts will be performed in duplicate, with discrepancies resolved by consensus. Screened references will be selected for full text review if the title or abstract indicates the document may contain relevant information. Full-text review will be undertaken in duplicate with a third reviewer consulted to resolve any discrepancies. Authors will be contacted for full-text where it is unavailable. If insufficient data are reported, authors will be contacted to request this. Risk of bias in individual studies will be assessed using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions: www.riskofbias.info/welcome/home) for observational studies and the Cochrane Risk of Bias 2 tool for randomised controlled trials, both of which we have used previously[60].

Outcome data from eligible intervention studies will be extracted into a purpose-built database in Microsoft Excel. All extracted data will be categorized by:

- **Location of the intervention**: e.g. prison, drug treatment centres, pharmacy, accident and emergency, homeless shelter, fixed site needle and syringe programmes, and mobile outreach.
- **Primary intervention outcomes**: whether to improve testing uptake, linkage to referral, or treatment initiation and success.
- **Types of intervention components**, including categories that either: increase staff resources (nurse, peer or key-worker) and/or staff education and awareness to improve testing and referral to treatment; allow treatment in community settings to improve referral, treatment initiation and success, e.g. through task shifting to nurse-led treatment, possibly with periodic clinician-led clinics in community settings; simplify the pathway of care through fewer visits, tests or the use of point of care diagnostics; incentives or targets to improve outcomes.

Some interventions will contribute to multiple outcomes and have multiple components, such as the HepCATT intervention described previously, which increased testing uptake and referral to treatment through increasing staff resource (a nurse) in drug treatment centres. Other interventions similar to this now also allow nurse-led treatment in drug treatment centres (41). Also, some interventions may be a subset of others, such as using point of care tests to simplify the pathway of care in nurse led interventions in drug treatment centres. In these cases, the intervention will be categorised in the broader intervention type (nurse led interventions in drug treatment centres), and the evidence synthesis will assess whether this addition to the intervention improved outcomes.

We will assess all studies in a category of interventions for relevance to a contemporary English setting (decided through expert consultation), and also for study quality. Those studies considered to be sufficiently relevant will be included in the synthesis used for our modelling. If there are sufficient studies for each intervention category, we will test for heterogeneity (using I^2 and meta-regression). If there is evidence of heterogeneity, we will report results from the random effects model, otherwise reporting results from the fixed effect model. Meta-regression and/or sensitivity analyses will be used to assess factors that affect outcomes of the interventions, such as use of point of care tests to improve linkage to care for nurse-led interventions in drug treatment centres. From considering existing studies already identified in the UK (see Review of Evidence section), it is likely that there will be multiple studies for some interventions (e.g. opt out testing in prison, nurse-led interventions in drug treatment centres) but possibly single or few studies for others (e.g. mobile outreach to increase testing for homeless PWID or pharmacy based testing and treatment interventions). Sensitivity analyses will also assess whether excluding studies with high risk of bias (e.g. before and after studies) influences our findings.

The UK costs of each intervention category or intervention type selected for inclusion in the modelling will also be estimated. This will be achieved through a number of steps as it is unlikely the necessary information will be available from a single source (e.g. the literature). Firstly, resource use will be estimated using a combination of information from the ODNs, through a survey / questionnaire and follow-up conversations to capture the inventions that are performed, the way in which these interventions are designed (e.g. how testing is delivered and by whom), and the resource use associated with each intervention. If the primary data collected from the ODNs are not sufficient, or if it is not possible to estimate the cost associated with testing from this data, then we will utilise a literature search by revisiting the relevant articles / abstracts identified in the literature review of outcome data, and also contacting the authors if required. If relevant resource use information cannot be identified using either of these two approaches, then assumptions will be made using expert opinion. Where necessary, NHS and social care unit cost information will be used to value the resources (60, 61), supplemented by information from the ODNs and the literature if required (see Table 2). Using these estimated resource use and cost estimates, we will produce a template for the estimated resources needed and associated costs of each type of intervention. Sampling bounds will be associated around these cost estimates based on whether there is uncertainty

Through this synthesis, we will produce cost and effect estimates for different intervention categories or types. As an example of the type of data we expect to identify, a recent evaluation of an intervention that placed a nurse facilitator in drug treatment services to improve HCV testing and linkage to treatment (HepCATT) suggests it increased testing 3-fold and treatment referral 10-fold(25). Costing data suggests fixed costs of £42,000 (training, overheads, and management) per site and costs per PWID tested or engaged of £115-161 and £460, respectively.

Methods for AIM 2: economic modelling

Decision problem and design features: This project will assess the impact and cost-effectiveness of different combinations of case-finding, linkage to care and treatment strategies for PWID, using a decision modelling approach. The model will be used to determine the optimal mix of case-finding, linkage to care and treatment interventions to reduce HCV incidence by 80% in England by 2025 or 2030. We will do this for 4 selected ODN regions that represent a spread of settings, with comparisons across these regions and sensitivity analyses being used to determine the optimal strategies for the remaining 18 ODNs.

We will use a dynamic model of HCV transmission and disease progression among PWID and former PWID that properly accounts for both disease morbidity and prevention benefits of HCV case-finding and treatment. The modelling is split in to three parts. In **PART 1**, the model will be calibrated to 4 ODN regions to assess whether the existing provision of services will achieve the elimination goal. If existing strategies are insufficient, then in **PART 2**, each ODN model will be used to evaluate the cost-effectiveness of different scenarios of either scaling up existing case-finding, linkage to care and treatment strategies, and/or initiating alternative strategies undertaken elsewhere. This will use data from AIM 1 on the costs and outcomes of these strategies. Intervention scenarios will be compared to determine the impact and most cost-effective strategy for different budget levels (including local budget levels), and the least costly strategies for achieving the NHS-England elimination goal for incidence in that ODN. In **PART 3**, we will undertake sensitivity analyses to support other ODN areas by generating simplified economic models for each ODN.

Regional collaborative groups (including ODN clinical leads, NHS and drug service providers, Public Health England staff, local government, and patient representatives) will be formed to guide the modelling for each ODN, including a range of interested people that have relevant expertise. The ODN lead and manager will help us form these groups. These groups will advise on how ongoing case-finding, linkage to care and treatment strategies could be improved and which new strategies could be initiated. They will facilitate access to local data for our modelling and will critically appraise our modelling to ensure it accurately portrays their ODN. They will support the formation of a local PPI group and will help disseminate and operationalise the model findings in their region. These collaborations will ensure ODN buy-in, so maximising the impact of our modelling on their decision making.

We will hold at least 3 collaborative meetings in each ODN (see Gant chart) and involve representatives from each regional collaborative group in our expert steering group. The **first** meeting will discuss the project aims and data requirements for our modelling; the **second** will provide feedback on our preliminary modelling of the impact of existing interventions, and will discuss which new interventions options are needed and could be introduced; and the **third** meeting will discuss our projections of the most efficient interventions that could achieve elimination. These discussions will assess the practicability and feasibility of scaling up existing strategies and/or introducing alternative interventions.

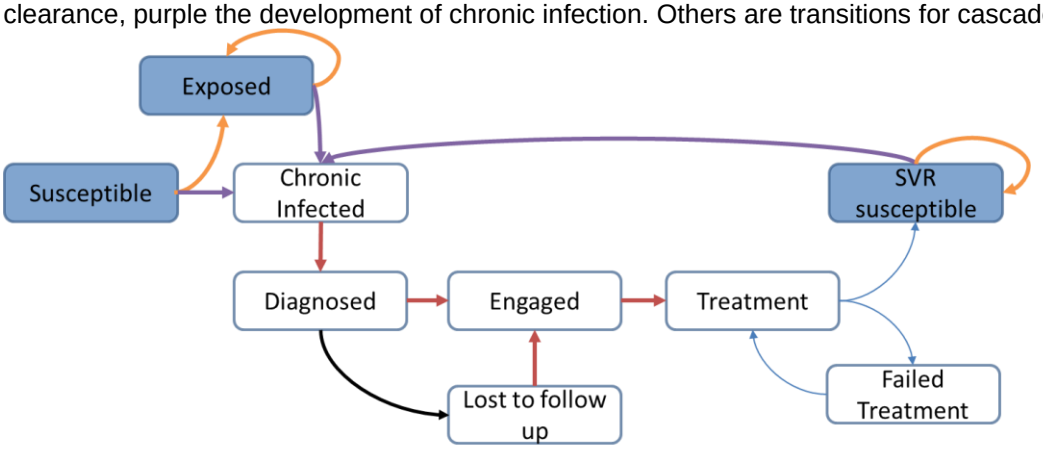
Model Description: We will develop an open dynamic deterministic model of HCV transmission and disease progression among PWID and former PWID that incorporates case-finding, linkage to care interventions and treatment. This model will be similar to previous models of HCV and case-finding that we have developed for the UK (62, 63). The model simulates the movement of current PWID through different strata of injecting duration (recent, non-recent and long-term injectors), HCV infection (susceptible, acute and chronically infected) and disease states (Metavir fibrosis stages F0 to F3, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant and post-liver transplant), and service contacts through which diagnosis and treatment can occur. These will include drug treatment services, needle and syringe programs, prison, primary care, A&E, and homeless services. Stratifications by injecting duration are included to allow increased incarceration(64) and injecting cessation (65, 66) among people recently initiated into injecting, as well as potentially reduced treatment uptake(7), with the chosen stratification in line with reporting from the unlinked anonymous monitoring (UAM) survey of PWID (13).

New initiates to injecting are susceptible to HCV and become infected in the community or prison at rates dependent on the prevalence of infection. PWID on opioid substitution therapy or needle

and syringe programmes have reduced risk of HCV infection(67) while recent incarceration (68, 69) and current homelessness(70) increases transmission risk. Once infected, some PWID spontaneously clear infection (71), with the remainder becoming chronically infected, which is life-long unless treated. Chronically infected PWID progress through disease states, with HCV disease progression being modelled as in previous models(62)including progression and death rates from two meta-analyses (72, 73). Death also occurs due to drug related causes with mortality rates coming from 2 UK studies (65, 74). HCV treatment occurs at rates dependent on levels of case-finding in different settings and resulting linkage to treatment (see next paragraph). Successful HCV treatment results in a sustained virological response (SVR, effective cure), with this halting disease progression(75, 76) except for those with compensated cirrhosis (progression at slower rate (75, 77)) or more severe disease(78-80). Re-infection can occur among PWID that are cured. PWID cease injecting at rates dependent on their duration of injecting, with former PWID having continued disease progression if infected, the possibility of being treated and no risk of infection.

Some possible service contacts where case-finding, linkage to care and treatment interventions can occur will be modelled as specific states (prison, drug treatment services, needle and syringe programs and homelessness) which PWID can transition into. Case-finding/testing will occur from these different states at specific rates depending on levels of case-finding occurring in these settings in a particular region. Additional case-finding will also occur from these states (on drug treatment services and/or needle and syringe programmes, being homeless) through other modalities (GP, secondary care or A&E testing) depending on the frequency that different sub-groups of PWID attend those services (normally for other reasons). For example, PWID could be tested through attending drug treatment services, while they could also have a frequency of attending GP surgeries, secondary care, or A&E where they could also be tested if case-finding initiatives exist in those settings. Incarcerated PWID will be assumed to only be tested through in-prison case-finding. The cascade of care will be included for each modality of case finding, with HCV infected PWID being subdivided into undiagnosed or diagnosed, with those who are diagnosed either being engaged or linked to care, on antiviral treatment, SVR and susceptible (cured), or failed treatment (non-SVR - not cured). Individuals can also be lost to follow up. A model schematic for the cascade of care aspect for any modality of case-finding can be seen in Figure 1.

Figure 1: Model schematic for cascade/pathway of care for each modality of case-finding.
Blue boxes denote susceptible while white boxes denote chronic infection. Orange arrows denote spontaneous clearance, purple the development of chronic infection. Others are transitions for cascade of care.

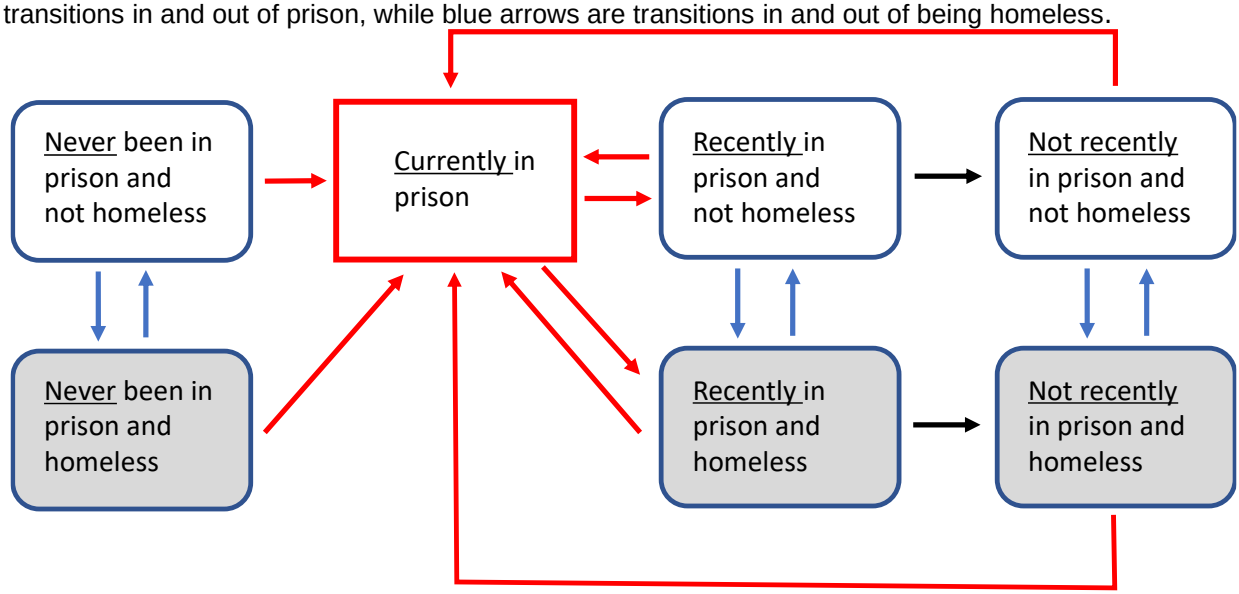


The intervention states (and potential case-finding setting) of attending needle and syringe programs (NSP) or opioid substitution therapy (OST or drug treatment services) will be incorporated in the model as in previous models(62), with PWID being stratified into no OST or NSP, OST only, NSP only, or both. PWID will be recruited on to OST or NSP at specific rates to give observed coverage levels, with cessation rates from OST and NSP being based on UK data (65, 81). We will assume OST and NSP reduce the risk of HCV acquisition and transmission as found in a recent Cochrane Systematic review[60]. Similarly, incarceration and homelessness will be modelled as in the schematic in Figure 2, with incarceration including strata for currently in prison and recently (within last 6 months) or non-recently released from prison. These strata are included because previously incarcerated PWID have higher reincarceration rates(64) while recently released PWID have heightened HCV acquisition risk (68). PWID are incarcerated or reincarcerated at rates which vary by duration of injection and are

released at rates based on the duration of incarceration among PWID in the UK (unlinked anonymous survey dataset and (64)). Lastly, the initiation rate of becoming homeless will be specified to give observed levels of homelessness in PWID, with cessation rates from homelessness being based on UK data (82).

Although complex, we have shown our ability to develop, calibrate and effectively use models such as these in numerous previous analyses for the UK(62, 63).

Figure 2: Model schematic for the incarceration and homelessness aspect of the model
Blue boxes denote not currently in prison with grey shading denoting currently homeless. Red arrows are transitions in and out of prison, while blue arrows are transitions in and out of being homeless.



Model data sources: For each ODN, the model will be parameterised and calibrated using national datasets, including the **Unlinked Anonymous Monitoring (UAM) survey** of PWID, **sentinel surveillance of HCV testing** and **HCV treatment database**, and regional data from each ODN.

- The **Unlinked Anonymous Monitoring survey** is a yearly bio-behavioural survey among PWID (n=1514 in 2017) attending low threshold needle and syringe programmes (NSP) or drug treatment services, ongoing since 1990. The survey includes data on drug use behaviours, intervention uptake, recent and ever incarceration, duration of last incarceration, current and ever homelessness, health service contact in last year (GP, A&E, pharmacy, prison health), time since last HCV test, location of last HCV test (drug treatment services, prison, pharmacy, A&E, homeless shelter, GP), diagnosis status, and whether they received HCV treatment when they tested positive. HCV antibody and RNA testing is also undertaken to determine the prevalence of current and previous infection, which is being used to monitor reductions in chronic prevalence due to treatment. For each ODN, the Unlinked Anonymous Monitoring survey will be used to characterise the ongoing and past HCV epidemic (HCV prevalence over time and against duration of injecting), levels of intervention coverage (current NSP and drug treatment services), incarceration (recent and ever) and homelessness (current). In combination with the next 2 datasets, it will also provide data on ongoing rates of HCV testing for different testing settings and estimates of current HCV treatment uptake. For estimating the utility of different health services for scaling up testing in each ODN, data on which health services (GP, hospital, A&E, prison health etc..) PWID have accessed in the last year will also be used. Because sample sizes will be small for some ODN and certain sub-analyses, data will be pooled over neighbouring ODN (or wider English regions) and/or multiple years (2-4 years) when necessary. This issue has been minimised by selecting ODN regions with larger Unlinked Anonymous Monitoring survey samples. According to data obtained from Public Health England's UAM team (30th June 2019), the Nottingham ODN had a UAM sample of 166 in 2017 and 192 in 2018. Bristol ODN had 182 in 2016, 64 in 2017 and 232 in 2018. Manchester ODN had 99 in 2016, 51 in 2017 and 146 in 2018. West London ODN had 90 in 2017 and 115 in 2018. Including data from 2018, all our selected regions have >100 samples per year. Recent

model analyses by our team(69) illustrate the utility of using this dataset for parameterising and calibrating sub-national models in England.

- The **HCV treatment database** records data on **all** HCV treatments (new direct acting antiviral therapies and other) and outcomes undertaken in England since 2015 (n=24,592 by 30 April 2018 (11)). The dataset records demographic information (gender country of birth, ethnicity and age), disease stage, mode of transmission (e.g. current and ever injecting drug use), testing and treatment location (prison, GP clinic, drug treatment services, A&E, secondary care), previous treatment, co-morbidities, provider and ODN region where treatment occurred. For each ODN, this data will be used to estimate on going levels of treatment among PWID for different testing and treatment locations, levels of treatment completion for PWID, and their sustained virological response (cure rate). Treatment numbers from this dataset will be combined with new PWID size estimates for each ODN region(83) to estimate the proportion of HCV-infected PWID that are being treated each year.

- The **sentinel surveillance of HCV testing** collates data on venous and dried blood spot testing for HCV in England through direct extracts from PHE/ NHS laboratories, covering about 40% (418,199 tests in 2017) of all tests undertaken among the GP registered population(14, 84). The dataset records testing location, test result and whether confirmatory RNA testing was done. The sentinel surveillance is being linked to the **HCV treatment database** (ready mid-2019), which will enable us to construct the **full** cascade of care for different testing locations[14] in each ODN. This data on the cascade of care will be combined with similar data from the unlinked anonymous monitoring survey to parameterise this part of the model for each ODN.

- For each ODN, we will map out ongoing case finding strategies for PWID, obtaining data on where testing and treatment is being done, and how. This will enrich data from the sentinel surveillance of HCV testing and unlinked anonymous monitoring survey to give a better understanding of where testing and treatment is being done and what other initiatives could be considered. Through mapping the care pathways and resources used by each testing and treatment initiative, we will estimate their costs using the methods in AIM 1.

The first three datasets are managed by Public Health England (PHE). Aggregated and/or anonymised data from these datasets will be accessed with appropriate permissions from PHE through co-applicant Sema Mandal and other collaborators who manage these datasets (Ellen Heinsbroek). Lastly, historical data from other local community surveys (69) will supplement data from the unlinked anonymous monitoring survey for calibrating trends in HCV prevalence, incidence, incarceration, homelessness and intervention coverage. Also, the national drug treatment database (managed by PHE), and a recent linkage of this database with ministry of justice data(85) will help parameterise the model's dynamics of incarceration and give additional data on levels of drug treatment to critique estimates from the unlinked anonymous monitoring survey (which can be biased).

Model parameterisation: In **PARTS 1 and 2**, the model will be parameterised and calibrated to data from 4 specific ODN regions as described in the previous section. These ODN were chosen based on their geographical spread, good coverage of the unlinked anonymous monitoring survey and sentinel surveillance, enthusiasm of the ODN lead in being involved, and varying modalities and intensity of case-finding going on, with Table 3 summarising some of the key data available for these ODN from the datasets described above. The possibility of including a mainly rural ODN region (with coastal populations) will also be considered following discussions with co-applicants, assessment of data availability, and after approaching relevant ODN clinical leads to assess interest and feasibility. This option is being considered because rural regions are likely to require different testing and treatment strategies, while some coastal towns have recently been found to have increasing drug related harms and high HCV prevalence (Blackpool- 80% Ab prevalence in recent UAM surveys).

Table 3: Summary of data available for PWID from each ODN. All data from UAM except estimated number of PWID (83) and estimated number PWID treated 2015-2018 (HCV Treatment database)

ODN region	Number current PWID	HCV sero-prevalence	% tested last year	% diagnosed	Number PWID treated 2015-18	NSP coverage	OST coverage	% ever in prison	% recently homeless
Greater Manchester	8900	64%	38%	45%	253	61%	82%	77%	44%
Nottingham	8840	55%	37%	42%	176	75%	69%	74%	50%
Bristol and Severn	6180	63%	41%	50%	433	66%	61%	67%	63%
West London	3390	66%	40%	46%	112	69%	81%	65%	42%
North Central London	6250	61%	34%	64%	55	47%	87%	72%	44%

OST: Opioid substitution therapy; NSP: Needle and syringe programmes; UAM unlinked anonymous monitoring survey. Percentages refer to the estimated percentage of PWID in that ODN region that report specific intervention contact (currently on opioid substitution therapy or have high syringe coverage), or that have ever been in prison, recently homeless, have a diagnosed HCV infection, or have a positive HCV antibody response.

Other than the datasets above, data from the literature will also be used to parameterise the model, with details given in the model description.

Baseline model calibration: Because of uncertainty in the data used to parameterise and calibrate our model, prior distributions will be assigned to all important model input parameters, and Bayesian methods will be used to generate multiple model fits to available data for each ODN. This will include calibrating the model to temporal trends in HCV prevalence by duration of injecting and differences in HCV prevalence by incarceration status (to aid in parameterising the increased risk associated with recent incarceration). The model will also be calibrated to temporal trends in the coverage of OST and NSP over time, levels of ever HCV diagnosis and treatment over time (overall and for different settings), prevalence of homelessness and dynamics of incarceration.

Importantly, some parameters will have informative priors based on existing data estimates while others will be wholly estimated through the model fitting because no estimates exist. To ease the calibration process, the model is likely to be fitted in two steps as done in recent models including prison dynamics (64, 86). **Firstly, the dynamics of incarceration, homelessness, injecting cessation and coverage of NSP and OST will be calibrated**. As already done in Scotland(64), the incarceration aspect of the model will be calibrated to self-reported data from the unlinked anonymous monitoring survey on the proportions of community PWID who have never been incarcerated, incarcerated once or multiple times by duration of injecting to estimate the primary incarceration rate and re-incarceration rate which have no data estimates. Simultaneously, the homelessness, OST and NSP dynamics of the model will also be calibrated to self-reported data from the unlinked anonymous survey on the prevalence/coverage of PWID in these states over time, with this calibration being used to estimate the rates of becoming homeless or initiating OST and NSP, while assuming prior distributions for the rates of leaving OST, NSP and homelessness from the literature (81, 82, 87). Importantly, we will allow the rates of becoming homeless and initiating OST and NSP to vary by different PWID sub-groups if data from the unlinked anonymous monitoring survey suggests there is heightened homelessness among PWID that have recently or ever been incarcerated and/or reduced coverage levels of OST and NSP among PWID that are homeless and/or recently released. Preliminary analyses suggest this may be the case. The injecting initiation and cessation rates used in the model will also be estimated through calibrating the model to the estimated number of PWID in each ODN and the proportion of PWID in each injection duration category from the unlinked anonymous monitoring survey, as done in previous modelling in the UK (62). **Secondly, the dynamics of HCV transmission and treatment will be calibrated**. The HCV transmission aspect of the model will be calibrated to the overall trends in prevalence of HCV over time, and differences in HCV prevalence by never or ever been incarcerated, and by different durations of injecting, as done similarly in previous analyses (62, 64). This calibration will estimate the baseline HCV transmission probability for PWID not on any intervention and not homeless or ever incarcerated, and will modify the literature estimated prior ranges for the heightened relative risk of HCV transmission among homeless PWID, recently initiated PWID and recently incarcerated PWID, and reduced relative risk of HCV transmission among PWID on OST and/or NSP. The model will also concurrently be calibrated to overall trends in HCV treatment, and by testing and treatment setting, with this calibration modifying prior ranges for the rate of testing

and linkage to care for different testing locations as estimated from the datasets described above. The dynamics of treatment will also affect the HCV prevalence dynamics, especially in recent years when treatment started to scale up.

As in previous analyses, we propose to use Approximate Bayesian Computation (ABC (64)) to calibrate the model for each ODN. This algorithm uses multiple rounds of parameter selection and filtering to approach the posterior parameter distributions through successive reductions in tolerance until a final pre-specified tolerance is reached. Model calibration will be computationally intensive and require Super Computer facilities at the University of Bristol which the team has experience of and exclusive access to a proportion of. Following the ABC, parameter fits for the model will be accepted if the simulated data falls within the 95% confidence intervals of the specified calibration data. These model runs are defined as the **baseline model fits** which will be used for all analyses.

Table 4: On going case-finding and treatment strategies in each ODN. Obtained from ODN leads.

Is screening and on-site treatment done in each settings?	Bristol		Manchester		Nottingham		West London	
	Screen	Treat	Screen	Treat	Screen	Treat	Screen	Treat
Drug treatment centre								
Pharmacy OST clients								
Pharmacy NSP clients								
Fixed site NSP								
Homeless shelter								
Outreach to homeless								
Accident and emergency								
Prison screen on entry								
Prison mass screen								
GREEN cell denotes high coverage, **ORANGE** cell denotes low coverage pilot, **RED** denotes not being done; NSP: Needle and syringe programme; OST: Opioid substitution therapy								

Analyses for PART 1 – Impact of existing interventions: For the ODN regions in Table 3, the **baseline model fits** will be used to estimate the impact of on-going testing and treatment strategies in that setting. A brief summary of ongoing interventions in each ODN are given in Table 4. This modelling will assume that existing levels of testing and treatment continue at the same levels (as the model was parameterised/calibrated to), with the model assessing whether the HCV elimination target for incidence (80% reduction in incidence from 2015 to 2025 or 2030) will be achieved in that ODN with current levels of testing and treatment, and when that would occur. We will consider the incremental impact of existing testing and treatment strategies by comparing the impact achieved for the baseline model fits from 2015 to 2020, 2025 and 2030 with counterfactual model runs that adapt each baseline model fit by assuming the expansion of direct acting antiviral treatment among PWID did not occur from 2015. These analyses will also consider whether the elimination target for incidence could be reached with a reduced range of testing and treatment strategies at lower costs (estimated in PART 2). Impact will be estimated in terms of relative difference in HCV incidence and prevalence at 2020/25/30, and percentage of infections or deaths averted over 2015 to 2020/25/30.

Analyses for PART 2 – Cost-effectiveness of expanding interventions: For each of the ODNs, we will evaluate the cost-effectiveness of different scenarios of scaling up and/or adapting on-going case-finding, linkage to care and treatment strategies, and/or initiating new strategies that have been done elsewhere. These scale-up scenarios will use data on the costs and effects of different interventions from the systematic review in AIM 1 and estimated for each ODN, with the reach of specific strategies being dependent on the likelihood that PWID have been in contact with different services in the last year (drug treatment, NSP, prison, GP, A&E, pharmacy – unlinked anonymous survey data). Specific focus will be given to determining which strategies are needed to reach those with low testing and treatment coverage through existing strategies (identified through the UAM survey and PPI input), such as the homeless. Costs for the 'old' standard-of-care treatment pathway, which generally involved screening in primary care or drug treatment centres with passive referral to secondary care for treatment, have been estimated in our on-going analyses. Intervention scenarios will also consider improvements in the coverage of OST and NSP to optimal levels to see how that effects the cost-effectiveness of different case-finding and treatment interventions through minimising re-infection, with cost estimates for OST and NSP coming from existing analyses(69, 88).

For each scale-up scenario, the costs and impact of improving case-finding and treatment outcomes will be compared to on-going/existing strategies. We will follow NICE Technology Appraisal guidelines for the economic analyses (89) except we will assume a combined service provider perspective. The cost-effectiveness of each intervention will be evaluated by estimating the incremental cost-effectiveness ratio (ICER) in terms of mean cost per quality adjusted life year (QALY) gained. This will assume a provider's perspective, a 50-year time horizon and a 3.5% discount rate for both costs and outcomes in the base-case. Health care costs and utility weights relating to HCV disease stages will be taken from previous economic analyses(90, 91). Probabilistic uncertainty analyses will be used to estimate the uncertainty in the impact projections and around the incremental cost-effectiveness ratio, accounting for uncertainty in the intervention effects and costs, as well as uncertainty in behavioural and epidemiological inputs. The estimated ICERs will be compared against NICE's willingness to pay thresholds for intervention's being cost-effective in UK (£20,000 per QALY saved (89)).The probability that each intervention is cost-effective will be estimated and we will generate cost-effectiveness acceptability curves. Sensitivity analyses for key parameters will be undertaken, with analysis of covariance methods being used to summarize the proportion of the variability in the impact projections, incremental costs, and QALYs gained explained by the uncertainty in input parameters (92). Univariate sensitivity analyses will consider such things as changes in the time horizon (25/50 years), discount rates, changes to the intervention costs and effects, and coverage of the intervention.

For each ODN, the mean incremental costs and impact of different intervention combinations will also be plotted on the cost-effectiveness plane to identify the cost-effectiveness frontier that connects the most cost-effective intervention combinations and shows which interventions are dominated by more cost-effective options and so should not be considered. This determines the order in which interventions should be used or scaled up to increase testing and treatment coverage through choosing those combinations that are most cost-effective for that level of investment. Through doing this, we will be able to map out what is the best that can be achieved with different levels of investment, and which strategies can scale up HCV treatment sufficiently to achieve the WHO and NHS-England elimination target of reducing HCV incidence by 80% by 2025 or 2030.

The strategies that can achieve elimination will be ranked according to their overall cost and QALYs so that we can see which interventions will achieve elimination for minimal cost. Uncertainty in important parameters (yield, linkage to care and cost of different case finding interventions, degree to which PWID can be reached through specific settings where testing occurs) will be incorporated into these model projections so that we can estimate the probability that specific intervention combinations are on the cost-effectiveness frontier or the probability that they are the cheapest option for achieving the elimination target.

Note, if the model already suggests that existing testing and treatment strategies will achieve elimination (PART 1), then the modelling in PART 2 will focus on determining the cost-effectiveness of existing strategies, and whether certain strategies could be stopped to reduce costs while still achieving elimination.

The outcomes of these analyses will guide decision-making going forward in each ODN. They will be essential for understanding which case-finding, linkage to care and treatment interventions are the most efficient use of resources and which can achieve most impact if scaled up or maintained. Through doing this in collaboration with the regional collaborative group in each ODN, we will produce a roadmap for how they should scale-up case-finding and treatment interventions to eliminate HCV in their ODN, the likely costs of doing so, and the cost and health implications of choosing these options compared to others. This will prevent the allocation of funds to interventions that are not needed for reaching elimination, while also producing recommendations on the required coverage of chosen interventions for achieving elimination.

Analyses for PART 3 - Generalising to other ODNs: Any differences in the optimal strategies across the 4 ODN regions will be critiqued to determine what parameter differences resulted in the distinct outcomes. Further sensitivity analyses will assess the importance of other context specific variables (that differ across the 22 ODN regions) for changing the resulting optimal case-finding and treatment strategy. Amongst others, these could include the coverage or potential reach of existing or new case finding and treatment strategies, variations in the cost or effectiveness of interventions, the coverage of OST and NSP, existing levels of incarceration and homelessness, and the prevalence of chronic HCV infection, all of which will be varied over their respective ranges across the 22 ODN regions. These sensitivity analyses will also account for important differences that exist in specific settings, such as

differences in the availability of services in rural regions or evolving drug use epidemics or high HCV prevalences in some coastal towns. Specific ODN-like scenarios will then be developed that capture the main characteristics of each ODN shown to be important in these sensitivity analyses. This mapping will involve estimating specific parameters for each ODN. Much of this data will be available from the datasets described above but will also include additional summary data on existing case finding and treatment strategies being undertaken in each ODN, which will be obtained through ODN clinical leads.

The modelling results from the original 4 ODN regions and these sensitivity analyses will be presented and shared with other ODN leads to get feedback on how they relate to decision making in their ODN. This will be used to get input on what additional sensitivity analyses or changes are needed to generalise the results to all regions in England. Following these additional sensitivity analyses, the resulting model projections will be used to produce guidelines on what case-finding, linkage to care and treatment strategies should be employed in each ODN to achieve HCV elimination. Similarly to PART 2, these results will guide other ODNs' decisions on what strategies to employ to increase testing and treatment, giving broad guidelines on the priority level of different intervention strategies for scaling up testing and treatment in their regions, and the likely impact that each will achieve. These will be disseminated to ODN leads, with interested regions having the opportunity to further modify our assumptions for their region, allowing them to tailor the model projections to their setting to maximise its relevance to their decision making.

6. Project timeline

The planned timeline for the project is given in the table below although it is likely that this will be extended due to delays in Year 1 due to Covid-19. We will adapt timeline when we have a better idea of how much the project will be delayed. In summary, AIM 1 (systematic review and evidence synthesis) will be done in year 1, PART 1 and 2 of AIM 2 (modelling for 4 ODN) will be done in years 1 and 2, with PART 3 of AIM 2 (generalisation to other ODN) being done in years 2 and 3.

		2020				2021				2022			
Aim	**Task**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
1	Update PHE systematic review (TBA1&2)												
1	Synthesise outcome and cost data for interventions (TBA1&2, JW)												
1	Produce effect and cost templates for interventions (TBA1&2, JW)												
1/2	Regional collaborative meetings (All)												
2	Model development - **done before grant (ZW) under other funding**												
2	Data analyses of regional and national datasets for model (TBA1)												
2	Collate data from 4 ODN on existing case-finding and treatment strategies (TBA1&2, JW)												
2	Parameterise and calibrate model to 4 ODN (ZW)												
2	Model projections of impact of on-going strategies in 4 ODN (ZW)												
2	Cost-effectiveness projections of how should scale-up in 4 ODN (ZW, JW)												
2	Sensitivity analyses for generalising to other ODN (ZW, JW)												
The staff doing each task is given in the task column using following acronyms: Jack Williams (JW), Zoe Ward (ZW), PHE epidemiologist (TBA2), University of Bristol epidemiologist (TBA1). **Grey shaded cells** signify when work for that task will be done. PHE denotes Public Health England													

7. Ethics

The study we are proposing is essentially a cost-effectiveness analysis based on decision modelling techniques, where the majority of evidence will come from existing secondary sources, such as the literature and existing anonymised Public Health England databases. We also intend to engage with a

set of Operational Delivery Networks (ODNs), clinical leads and people who inject drugs or patient representatives/service users to derive some of the required information. The ODN members and clinical leads are included as co-applicants or collaborators on the proposal, thus they will be acting as specialist advisors for which ethical approval is not required. The patient representatives will be recruited from community-based drug treatment services through ODN members. In line with NIHR INVOLVE guidance (https://www.invo.org.uk/posttypefaq/do-i-need-to-apply-for-ethical-approval-to-involve-the-public-in-my-research/), ethical approval is not needed as the patient representatives will also act as specialist advisors involved in guiding the research and providing important insights based on their experience of Hepatitis C virus case finding and treatment services. This has been confirmed by the Health Research Authority.

8. PPI

Overview

Patient and Public Involvement (PPI) will guide the modelling undertaken during the project. The role of the PPI is to:

1. Inform the development and refinement of locally specific testing and treatment models for each ODN;
2. Gather feedback on model projections;
3. Inform dissemination and implementation of findings.

Three sets of PPI workshops (described below) are planned. Workshop 1 will discuss the limitations and inefficiencies of current case-finding, linkage to care and treatment strategies, while also giving feedback on new possible strategies with input from the systematic review. This will ensure our regional modelling accounts for the local needs and preferences of PWID. Workshop 2 will gather feedback on our projected optimal case finding, linkage to care and treatment strategies, to assess their acceptability and whether they would achieve sufficient coverage. Workshop 3 will focus on how to disseminate our findings to support improved HCV testing and treatment locally and nationally.

Workshop 1. Inform locally specific case-finding models

The approach to workshop 1 was piloted in Bristol with 7 PWID who use Bristol Drugs Project with experience of HCV infection, testing and/or treatment.

The agenda for workshop 1 will build on the approach used in the Bristol pilot and findings from the systematic review. It will explore knowledge of currently available testing and treatment strategies and which groups (e.g. homeless, recent incarceration) are reached or missed by them. Barriers and facilitators to service access will be explored to understand the strengths, limitations, gaps and inefficiencies of current local strategies. Lastly, feedback will be gathered on adaptations to existing strategies and new possible initiatives. The latter aims to identify what is still needed to improve the reach of case-finding initiatives and what would be the most successful/acceptable way to test and treat. The outputs from this workshop will inform team decisions about which strategies are eligible for consideration, which require improvement and where gaps in current testing and treatment coverage may exist.

Workshop 2. Feedback on model projections

The initial modelling projections for each region will be presented to that ODN's PPI group to gather feedback on the different options for optimal testing and treatment strategies. This will be used to assess their acceptability and whether they would provide sufficient coverage, i.e. would they miss certain sub-groups. This feedback will be used to improve and refine our local testing and treatment models and strategies and will inform the development of our cost-effectiveness analysis.

Workshop 3. Inform dissemination and implementation of findings

The last session will be a combined PPI group, which will focus on how to disseminate and translate the results into co-produced strategies capable of supporting improved uptake of HCV testing and treatment in each region, and more generally. Implementation strategies may include policy changes or educating key stakeholders and champions who can bring about change and engagement with service users and patients. The outputs from this workshop will help ensure that we develop recommendations for implementation strategies that are acceptable to PWIDs. This will result in the development of context sensitive recommendations for implementing the research findings.

Recruitment
We plan to hold PPI groups in each of the 4 ODN regions (Bristol, London, Manchester, and Nottingham) where we undertake modelling. The aim is to capture the variation in experience of case finding delivery across each ODN region. For example, involving people from urban and rural areas, and those engaged/not engaged with services. We will do this using extensive engagement with stakeholders (e.g. peer leaders) in key organisations across ODNs. Local stakeholders will facilitate the recruitment process by distributing information sheets to potential group members and discussing the project with them. People interested in participating will also be able to discuss the project with the research team. The information sheet will detail the purpose of the workshops and their involvement. Recruitment strategies will seek to mirror how the ODNs manage the diversity in their region. For example, Nottingham and Bristol are divided into urban and rural areas with mobile outreach for the latter areas whereas Manchester and London operate more centrally.

Ideally, we'd like to meet with a diverse group of 6 people who:

- Inject drugs
- Have varying levels of experience of hepatitis C testing and/or treatment either directly or indirectly (partners, family, associated)
- Have / haven't used the local drugs service
- Experience of homelessness and incarceration
- Male/female
- Range of ages

Reimbursement to group members
To enable these meetings, we will cover the time of each person involved in the PPI workshops at £22 per hour as set by People in Health West of England. We have found that this cost is sufficient to attract sufficient participants to previous workshops. We will also cover their travel expenses at £15 per person (to cover bus/train/car travel) and include £25 for each meeting to cover refreshments. Seeing we have already undertaken the first Bristol meeting, we will include costs for 8 workshops (2 in each ODN, but first already done in Bristol, and 1 central dissemination session) involving 6 PWID per workshop and lasts 2 hours. This gives a cost of £3032, or (8*25 + 8*6*2*22 + 8*6*15).

Workshop delivery
Group members will be asked to reflect on local testing and treatment services before the workshops. The workshop agendas will be developed in collaboration with all research team members to ensure their appropriateness and relevance. Agenda's will be applied flexibly to allow the pursuit of emergent topics and value the group members as the experts. Workshops will be conducted in a private space within an ODN specific location (e.g. local drug service) chosen for its convenience and safety to meet group members. Local ODN stakeholders will support the researchers conducting the workshops and ensure their safety. Workshops will be digitally audio recorded on an encrypted device to support note-taking. The audio recordings will be deleted at the end of the project.

Please note COVID-19 is likely to cause delays and disruption to the PPI work. In line with government advice, face-to-face research activities are not permitted by the University of Bristol at this time. The impact of the current situation on the PPI will be monitored throughout the project and appropriate adjustments will be implemented. While face-to-face PPI is preferred, we will endeavour to involve PWID in this project by other means if necessary. Remote options include using online platforms to run a workshop or conducting one-to-one discussions by telephone. The ability to conduct this PPI during the pandemic is also dependent on the capacity of ODNs to support it.

Ideally, we would like to engage with people who are currently injecting drugs and who may be missed by current services. These people are less likely to have access to the technology needed to make digital engagement possible. Digital engagement does not require access to a laptop or computer but would require some access to technology, e.g a smart phone. If the COVID-19 lock down makes involvement with this group of people unfeasible we will consider engaging with pre-existing groups that may have been set up by the ODNs or people who have recovered from drug

use. These people may be more likely to be able to engage digitally. We will review all options periodically as the situation develops.

Confidentiality
The research team will preserve the confidentiality of workshop members in accordance with the General Data Protection Regulation 2018. All information collected during the workshops will be handled according to the principles of the General Data Protection Regulation and University of Bristol data protection policies, especially for sensitive, personal information. Notes taken during the workshops will be anonymised and stored on a password protected computer located in the University of Bristol and appropriately backed up. If the researcher is concerned about information they hear from group members during the workshops, they will act in accordance with the local ODN services confidentiality policy. Relevant ODN stakeholders will be asked to provide these policies.

PPI guiding the modelling
Notes summarising each workshop and debrief meetings following the workshops will be shared with the research team at steering group meetings to ensure the regional modelling accounts for the local needs and preferences of PWID and their service provision. We will invite 2 PWID to our steering group meetings, and to 2 of our project team meetings each year. This is to enable them to contribute to the oversight and management of the project, including the PPI component, so ensuring their full engagement in the research project. We will invite Stuart Smith as a patient representative (Hepatitis C Trust) to some of the PPI workshops to enable his expert input.

9. Success criteria and barriers to proposed work

The main success criteria will be 1) the extent to which our recommendations are taken up by the operational delivery networks (ODNs) enabling a large scale up in treatment among PWID. Other success criteria will include: 2) completion of the literature review / evidence synthesis; 3) recruiting participants for the PPI focus groups and producing the required information from the meetings; 4) building and debugging the disease transmission decision model; and 5) using it to produce a set of policy recommendations with respect to the objectives.

The key risks include potential non-engagement by ODN members, other key policy makers, service providers and users. This is likely to heightened during the Covid-19 pandemic although NIHR have reassured that extensions will be granted to account for this. This could result in difficulties in accessing some of the required information in a timely manner and not having the intended policy and or operational delivery influence. Other risks include failing to derive the necessary intervention effects from the literature review, the need to build an arguably complex decision model, or producing results that are highly uncertain.

To mitigate these risks, Public Health England, national and regional Operational Delivery Network (ODN) members are involved with the study's design and are co-applicants on the proposal. The selected ODNs have demonstrated ability to collate and report on case-finding activities. Public Health England (PHE) has already engaged with the selected ODN clinical leads and managers and collected baseline information on case-finding and treatment approaches, capacity and resource use in their patch, thus providing reassurance that the selected ODNs can collate and report on case-finding activities. Furthermore, PHE HCV surveillance systems on new diagnoses and test positivity, the national HCV treatment database, and the unlinked anonymous survey of PWID have good coverage of the selected ODNs, such that these datasets can provide "remote" monitoring of on-going testing and treatment approaches which can supplement the information derived directly from the ODNs. However, if for any reason, a ODN no longer wishes to be involved, there have been numerous other ODN leads that have shown interest in this modelling, and so we will switch to another ODN.

PPI focus groups have been deliberately included to ensure that candidate interventions are appropriate for PWID needs. The expert steering group and regional collaborative groups will include leading clinicians, service providers, commissioners and PPI members, to help ensure the selected interventions and results are meaningful, policy relevant and implementable. The oversight committee will oversee the whole project.

Inspection of PHE's reviewing efforts to date shows that it will be possible to derive intervention effects from the literature, while our ongoing costing studies show that we will have sufficient cost data for a range of suitable interventions. On the modelling, we propose to adapt existing published HCV models that have been validated in the UK rather than starting completely afresh, so reducing the risk

in the modelling. This is an area where the PI has particular expertise, as evidenced by his numerous published modelling papers. If ultimately the results and recommendations are highly uncertain, which we do not expect, we will place greater emphasis on specifying relevant research recommendations and the value of performing these studies.

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