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TITLE: Hepcare Europe - Bridging the gap in the treatment of Hepatitis C: Study Protocol

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ABSTRACT:

Background. Hepatitis C (HCV) infection is highly prevalent among people who inject drugs (PWID). Many PWID are unaware of their infection and few have received HCV treatment. Recent developments in treatment offer cure rates >90%. However, the potential of these treatments will only be realised if HCV identification among PWID with linkage to treatment is optimised. This paper describes the Hepcare Europe project, a collaboration between five institutions across four member states (Ireland, UK, Spain, Romania), to develop, implement and evaluate interventions to improve the identification, evaluation and treatment of HCV among PWID.

Research design and methods. A service innovation project and a mixed-methods, pre-post intervention study, Hepcare will design and deliver interventions in Dublin, London, Seville and Bucharest to enhance PWID engagement and retention in the cascade of HCV care. The feasibility, acceptability, potential efficacy and cost-effectiveness of these interventions to improve care processes and outcomes among PWID will be evaluated.

Conclusions. Hepcare has the potential to make an important impact on patient care for marginalised populations who might otherwise go undiagnosed and untreated. Lessons learned from the study can be incorporated into national and European guidelines and strategies for HCV.

KEYWORDS: Hepatitis C, HCV, PWID, homeless, prisoners, screening, linkage to care, treatment, interventions, Europe

1. BACKGROUND

In the European Union (EU) and European Economic Area (EEA), approximately 5.6 million people have been infected with the Hepatitis C Virus (HCV) (1.1% of the general population). However, national estimates of seroprevalence vary widely, from 0.1% in Belgium, Ireland and the Netherlands to 5.9% in Italy (1). Approximately 50-80% of individuals infected with HCV will develop chronic infection which is associated with liver cirrhosis and hepatocellular carcinoma (HCC) (2, 3).

People who inject drugs (PWID) and ex-PWID bear the greatest burden of HCV infection in Europe and account for the majority of new infections. Estimates suggest that of 1.2 million current PWID in the EU/EFTA area, 0.7 million have been infected with HCV and 0.5 million are chronically infected (4). Prevalence varies substantially between countries: according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), HCV antibody (anti-HCV) prevalence among national samples of PWID in 2014–15 ranged from 16%-84% (5). Modelling studies predict substantial increases in liver disease among ageing HCV-infected PWID populations (6, 7).

Despite the high prevalence of HCV among PWID, many are unaware of their infection and few have received treatment. Estimates of undiagnosed infection among PWID in Europe range from 24%-76% (8). Among PWID diagnosed with chronic hepatitis C (CHC), the proportion entering HCV treatment is low (range 1–19%) (8). Low treatment rates are in part explained by the suboptimal referral of PWID post-diagnosis to specialist secondary care for evaluation and treatment of HCV (9), and also by poor attendance and defection from secondary care among those who are referred (10).

The World Health Organization's (WHO) recently developed Global Health Sector Strategy (GHSS) on viral hepatitis aims to eliminate viral hepatitis as a major public health threat, including the following targets for 2030 (11):

- Reduce CHC incidence by 90%;
- Reduce HCV-related mortality by 65%;
- Diagnose 90% of CHC infections;
- Treat 80% of eligible persons with CHC.

To achieve these targets, it is essential that countries increase prevention, testing and linkage of diagnosed individuals to treatment. As many PWID remain unaware of their infection and/or are not accessing HCV care, it is evident that new strategies to reach such individuals are necessary, including new testing strategies to increase the number diagnosed, and improved care pathways to ensure those diagnosed are successfully linked to HCV evaluation and treatment.

Previous research has identified a range of barriers to PWID accessing HCV screening, evaluation and treatment, including: anticipated stigma and discrimination, restrictions around HCV treatment eligibility, inconvenience of travelling to testing sites and hospitals, fear of HCV investigations and treatment side-effects, perceptions of HCV as relatively benign, being asymptomatic, and competing priorities (12, 13). Further barriers are a low level of awareness and HCV literacy among patients, healthcare providers, policy-makers, and the general public and limited attention, resources and commitment to HCV care at the political level (14).

Recent developments in HCV diagnostics and treatment can enhance access to, and uptake of, HCV care among PWID. Recently licensed point of care tests (POCTs) for HCV,

including rapid diagnostic tests (RDTs) from finger prick blood samples and oral secretions, are portable, easy to use and often less invasive than traditional venous blood sampling. Thus, they have the potential to make HCV diagnosis more available for many populations by facilitating outreach of screening beyond clinical settings and personnel. As most POCTs provide a result within 5-30 minutes (15), they may also enhance retention of patients in the subsequent cascade of HCV care.

Likewise, the replacement of liver biopsy by transient elastography (FibroScan^{TM}, Echosens, Paris), for the staging of liver fibrosis, enhances opportunities for the extension of specialist evaluation of HCV disease from hospital into community settings to reach more patients. In addition to being non-invasive, the FibroScan has advantages, including: (i) being portable, it can be transported to community sites to assess patients; (ii) individuals can relatively easily be trained in its use; and (iii) scans can be conducted within less than five minutes and results given immediately to patients, which may enhance their engagement with HCV treatment as previous studies have shown how clinical markers can impact patients' perceptions of HCV disease (12, 16).

However, the revolution in HCV treatment is the most significant advance in HCV care. The replacement of pegylated interferon and ribavirin with new interferon-free direct acting antiviral agents (DAAs) has reduced HCV treatment times to 8-12 weeks, improved safety profiles, and increased cure rates to >90% of cases (17, 18). These relatively simple, tolerable and highly effective treatments are improving treatment uptake among patients and enhancing opportunities for provision of treatment in community settings (19).

These developments in treatment make HCV elimination among PWID feasible (14). Modelling studies have shown that if treatment is delivered at the right scale, it can have a major preventative impact on HCV transmission (20). A challenge is the current high cost of the DAA treatments, which is a barrier even for high-income countries to deliver treatment at the scale needed. If price reform is not achieved, this could undermine countries efforts to impact upon the growing liver disease burden (21). However, even if DAA treatments were affordable and accessible to all, the full clinical impact of these therapies will be contingent on engaging and retaining PWID in the HCV cascade of care (22).

Attention now needs to turn to developing evidence-based, culturally appropriate strategies to improve diagnosis and linkage to care of PWID (14, 22). Several authors have argued that to optimise the potential of the new HCV therapies when they become more widely available, now is the time to scale up prevention, educate patients and healthcare providers, and identify the best interventions to enhance delivery of screening, assessment and treatment (14, 23).

A recent systematic review and meta-analysis of operational interventions to improve engagement and retention along the HCV cascade of care identified some effective strategies (22), including: reminders to clinicians regarding testing, HCV education and pre-test counselling accompanied by on-site testing, facilitated referral to specialist care, integration of mental health and substance misuse management with HCV treatment services, and nurse-led educational sessions about HCV treatment. This review did not restrict studies to PWID, although most studies were conducted amongst this population. A more recent systematic review which focused on PWID, people who use drugs and OST populations arrived at similar conclusions, including the effectiveness of dried blood spot (DBS) testing to enhance testing uptake (24). HCV treatment in almost all studies within both reviews was interferon-

based. Both reviews concluded that many of the studies were of low quality and further operational research is needed to optimise hepatitis care services (22, 24). The design and evaluation of interventions which simplify the HCV cascade of care in the new DAA treatment era, and which target multiple components within the care cascade, was identified as a research priority (24).

It is likely that multidisciplinary, integrated models of HCV care involving partnership between HCV specialists and community healthcare providers (14), and the continuing extension of HCV care into community settings, will be the appropriate foundation for HCV services adapted to the needs of PWID. The traditional location of HCV assessment and treatment in hospitals is a model of care ill-adapted to the needs and life circumstances of many PWID (14). At the same time, the limited infrastructure and HCV knowledge in OST clinics and primary care centres restrict their ability to provide HCV assessment and treatment unsupported (14). Thus, for the foreseeable future, a multidisciplinary, partnership approach is likely to be important. Various integrated care models have been demonstrated to successfully enhance HCV assessment and interferon-based treatment of PWID, including telemedicine clinics between specialists and primary care providers (25), and on-site HCV nursing and specialist support within OST clinics and community health centres (23, 26).

The epidemiological, demographic and socio-political situation with regard to HCV varies across Europe and there is diversity in countries programmatic responses to the epidemic (21). Comprehension of such issues and collaboration between key organisations and member states will be important for any chance of eliminating HCV (21). The relatively free movement of people between member states means that interventions will have greater effectiveness if countries work together and coordinate their activities. Collaboration and the

pooling of intellectual, research and political resources will hasten learnings regarding optimum HCV service provision.

Hepcare Europe is an EU-supported project involving collaboration between five institutions across four member states, including: University College Dublin (UCD), Ireland; Servicio Andaluz De Salud (SAS), Spain; Spitalul Clinic de Boli Infectioase si Tropicale "Dr. Victor Babes" (SVB), Romania; and University of Bristol (UoB) and University College London (UCL) in the United Kingdom. The project aims to develop, implement and evaluate interventions to improve HCV diagnosis, evaluation and treatment among PWID and linked groups such as prisoners and the homeless, across a range of settings in Dublin, Seville, Bucharest and London. We will develop outreach and integrated models of HCV care in the participating sites that are tailored to their health service infrastructure and population needs, to improve PWID engagement and retention along the cascade of HCV care. Interventions will include point-of-care diagnostics, nurse outreach, community-based evaluation of HCV disease, patient and healthcare professional education, and peer support. We will evaluate the feasibility, acceptability, potential efficacy and cost-effectiveness of the interventions within the different settings in order to provide a better understanding of how improvements to the care of PWID can be achieved.

1.1 Specific Objectives include:

Primary objectives

- To determine the feasibility, acceptability and potential efficacy of the various components of the Hepcare Europe package of interventions across the different settings to enhance HCV identification, evaluation and treatment among PWID and linked groups. Feasibility will be determined by examining the uptake of the

interventions across the different settings. Acceptability will be determined by examining participants' experiences of and satisfaction with the interventions. Potential efficacy will be assessed by examining the number and proportion of participants diagnosed, evaluated, treated, and attained SVR, pre- and post-intervention.

Secondary objectives

- To determine how the cost-effectiveness of the interventions might vary across different EU settings, and use the results to help guide decision criteria for when specific case-finding and care strategies should be used;
- To engage with key stakeholders, nationally and in Europe, to ensure our findings contribute to HCV policy and practice.

2. CONTEXT AND METHOD

2.1 Study Design and Settings

Hepcare Europe is a service innovation project and a prospective, observational, mixed-methods, pre-post intervention study.

Fieldwork in relation to the Hepcare interventions will take place in four sites (Dublin, London, Seville and Bucharest) and a health economics analysis will be conducted in the fifth site (Bristol). Taken together, participating sites have different histories and policies in relation to opioid substitution treatment (OST), harm reduction and access to the new HCV therapies and have different models of primary care (Table 1).

Dublin, Ireland

Estimates suggest 20,000-30,000 people in Ireland are chronically infected with HCV (27). Injecting drug use is the main risk factor in 80% of HCV cases (28). Studies indicate a prevalence of HCV antibodies (anti-HCV) among PWID of 62-81% (29-32). According to a recent study, between the years 1991-2014, an estimated 12,423 of approximately 16,400 PWIDs have been infected with HCV, with 9,317 chronically infected (27).

Methadone is the only form of OST prescribed in Ireland and is provided by addiction treatment centres, specialised GPs and in prisons (33). Ireland has three models of needle and syringe programmes (NSP), including: fixed site facilities, outreach syringe provision and pharmacy-based programmes (34).

National HCV screening guidelines have recently been published (35) identifying risk groups for screening, including PWID and linked groups such as prisoners and homeless people. The guidelines highlight that novel strategies and/or extra support may be required to engage prisoners and homeless people with screening and to enable their linkage to specialist HCV care and treatment. A National Hepatitis C Treatment Programme oversees access to DAA treatments on a phased basis. Until 2017, access was organised according to clinical need and restricted to those who were infected with HCV through blood and blood-products and those scoring >8.5 kPa on FibroScan. In early 2017 the criteria were revised to remove this threshold, but a limited healthcare budget and the high cost of DAAs continue to restrict the numbers who can avail of treatment.

The Hepcare Study in Dublin is taking place in two settings: (i) a closed, medium-security prison for adult males located in the centre of Dublin, which has the largest prison population in Ireland; and (ii) OST-prescribing GP practices in North Dublin. Both settings are within

the catchment area of the participating centre in Ireland, i.e. the Mater Misericordiae University Hospital, an academic teaching hospital in Dublin's North Inner City. The hospital's Infectious Diseases Department cares for a large number of patients with HIV and/or HCV.

London, UK

Estimates suggest approximately 214,000 people are living with CHC in the UK (36). Injecting drug use is the risk factor in 90% of HCV cases (37). Around half of PWID are thought to be anti-HCV positive in England (52%) and Wales (53%), with levels being lower in Northern Ireland (23%) and higher in Scotland (58%) (36).

In the UK, options for OST include methadone, buprenorphine, and rarely diamorphine. OST is delivered through specialist outpatient drug treatment services and shared care arrangements with GPs. NSP are provided mainly through pharmacies and drug treatment services, but also via street outreach workers and mobile van units (37). According to Public Health England's "*Shooting Up"* report, trends in injecting drug use in the UK are changing, with a growing number of people injecting amphetamines and amphetamine-type drugs such as mephedrone (38). There has been a recent sharp increase in HIV and HCV infections in South-West Wales linked to a move from opiate injecting toward injecting newly emerged drugs such as mephedrone (39). A HIV outbreak among PWID in Glasgow was also reported in 2015 (38).

In England, access to DAA treatments is organised by 22 Operational Delivery Networks who provide clinical leadership over a given geography and are responsible for delivering HCV treatment under certain conditions. NHS guidance in 2015 was that those with

Genotype 1 and cirrhosis, and those with decompensated cirrhosis (any genotype) were eligible for treatment with the new oral drugs (40). Eligibility criteria have since been relaxed and currently all genotypes regarding of stage of fibrosis are eligible for DAAs (41).

The Hepcare Study in London is taking place in two settings: (i) using the resources and Mobile Health Unit of the "Find&Treat" homeless health team of University College London NHS Trust, Hepcare will conduct outreach to selected sites within underserved communities in metropolitan London. Sites to be visited by the mobile van and/or screening staff will include homeless residential hostels, day centres and drug services; and (ii) OST-prescribing GP practices.

Bucharest, Romania

Approximately 489,000 people are estimated to have CHC in Romania (42). The majority of cases were infected nosocomially before 1990 (42). However, in the last decade there has been an increasing trend of HCV infections among PWID, with seroprevalence rates among PWID mounting from 47.6% in 2004 to 82.4% in 2012 (43).

HIV and Hepatitis B (HBV) infection among PWID also represent a challenge for the healthcare system. Rates of HIV and HBV were low among PWID until 2011, when an explosive increase in blood borne virus infections in drug users was reported, with HIV prevalence among PWID rising from 4.1% in 2010 to 49.2% in 2013, and HBV prevalence from 13.1% to 27.7% in the same period (44). This increase was driven by the replacement of heroin with new psychoactive substances called "ethnobotanicals", which have amphetamine-like effects, cause a high addiction and need for multiple administrations per day. This

change in injecting trends coincided with reduced funding of NSP and consequent shortage of clean needles (43, 45).

In Romania, OST (methadone, buprenorphine, or combination buprenorphine/naloxone) is delivered mainly through public medical units and Drug Prevention, Evaluation and Counselling Centres in Bucharest, as well as in prisons. One NGO and three private providers also provide OST. Coverage is considered low however, with an estimated 1 (<1-1) OST recipient per 100 PWID (46). NSP are provided by NGOs in Bucharest and two adjacent counties through outreach programmes in fixed locations and via street workers and a mobile team. Most injecting drug use is centred in Bucharest, where according to the latest reported data from 2013, there were an estimated 6288 PWID (43).

In 2014, supported by Norwegian Funds, a national project was initiated to create a national hepatitis registry. Secondary objectives of the project include testing for HIV and hepatitis in vulnerable groups, improving access to medical services and NSP for PWID, providing HCV education and training for healthcare professionals, and increasing public awareness of HCV, HBV and HIV.

Access to interferon (IFN)-free therapies is restricted in Romania. In 2015-2016, 5000 patients with compensated cirrhosis were treated with IFN-free regimens, while non-cirrhotic patients were eligible for IFN-based therapies only. Access was expanded in 2017 to decompensated cirrhotic patients, non-cirrhotic F3 patients, non-cirrhotic F2 patients with a contraindication to IFN-treatment, F2 patients with cryoglobulinemia, liver transplant recipients with recurrence of HCV, dialysis patients (F2-F4) and medical staff (47). In addition to restrictions relating to stage of fibrosis, patients with HIV/HCV co-infection are

required to give a negative drug test to receive reimbursed DAA therapy. However, those mono-infected with HCV do not seem to have the same requirement (41).

The Hepcare Study in Bucharest is taking place in a range of settings, including: (i) night shelters and NGOs caring for homeless people; (ii) OST centres; (iii) an inpatient drug treatment unit; and (iv) prisons. Patients from these sites will be referred to the participating center in Romania, i.e. the Victor Babes Clinical Hospital for Infectious and Tropical Diseases. The hospital serves a catchment of 50% of the Bucharest region and six additional surrounding districts and has been a centre for HIV / AIDS since 1989 (a University hospital since 1976).

Seville, Spain

Approximately 472,000 adults are estimated to have CHC in Spain (48). Over 300,000 individuals in Spain have a lifetime history of injecting drugs and estimates of HCV prevalence among PWID are 60-80% (49).

In Spain, OST (methadone or buprenorphine/naloxone combination) is delivered mainly through specialised outpatient drug treatment centres, some primary care centres, inpatient facilities and prisons. Harm reduction services are provided through social emergency centres, mobile units, pharmacies and prisons. Most harm reduction programmes include preventive educational interventions, NSP, BBV testing, and HAV / HBV vaccinations (50). Spain also has 13 facilities for supervised drug consumption (50).

In 2015, a National Strategic Plan for tackling HCV was published (51), consisting of four strategic directions:

- Establish the prevalence and epidemiology of HCV infection in Spain, promote early diagnosis in priority populations, primary prevention of HCV infection and secondary prevention of HCV-related complications;
- Define the scientific-clinical criteria for establishing the appropriate therapeutic strategy for CHC patients, including prioritizing those with most clinical need for initial access to DAAs;
- Establish coordination mechanisms to guarantee the implementation of the Strategy;
- Foster knowledge regarding HCV prevention, diagnosis and treatment in the National Health System.

The first strategic line of the Spanish Plan regarding early diagnosis has not been developed because all funding has been diverted towards the second strategic line referring to HCV treatment as a large burden of previously diagnosed infections are still pending treatment in Spain. Priority groups identified by the Strategy for DAA treatments include: patients with advanced liver fibrosis (F2-F4) or extra-hepatic manifestations of HCV, patients on transplant waiting lists, liver transplant recipients with recurrence of HCV, non-liver transplant HCV patients, and patients who have not responded to triple therapy with first generation protease inhibitors. In June 2017, access to DAA treatment was no longer restricted to priority groups. Currently, any HCV-infected patient can be treated with DAA combinations, regardless of fibrosis or any other clinical situation (41).

The Hepcare Study in Seville is taking place in a number of settings in the province of Seville, corresponding to the area of the participating center in Spain (i.e. the Hospital Universitario de Valme), including: (i) NGOs and other organisations dedicated to homeless people; (ii) drug addiction units; (iii) therapeutic communities; and (iv) OST prescribing

primary care centres. The Hospital is a tertiary care university hospital and its Infectious Diseases Unit is the premiere unit in the region.

2.2 Study populations, sampling and recruitment

The project is focused on three target groups:

(i) PWID at-risk of or diagnosed with HCV, and linked groups such as people who are homeless, sex-workers, and prisoners;

(ii) Healthcare providers working with the aforementioned groups, including: GPs, Practice Nurses, Counsellors, Social Workers and Outreach workers; and

(iii) Organisations involved in influencing health systems, including: national patient support groups, national bodies in participating countries, and key European and international bodies.

Population, convenience or purposive sampling will be conducted depending on the aims of the work package and setting.

2.3 Hepcare Work Packages

Hepcare Europe includes the following inter-connected work packages (WPs) (see Figure 1 and Table 2):

2.3.1 HepCheck

This WP will develop, implement and evaluate interventions to enhance HCV screening of PWID and linked groups, who although at risk for and often infected with HCV, are frequently marginalized in their engagement with health services. HepCheck will outreach screening to these groups through their points of contact with services in the community (e.g.

OST clinics, homeless services, prisons) and use a point-of-care testing strategy. A meta-analysis comparing HCV POCTs with reference tests found that on pooled analysis POCTs were highly accurate for diagnosing HCV, although authors cautioned care in the choice of test as the sensitivity and specificity of individual tests varied widely (52). HepCheck will use the OraSure Technologies OraQuick HCV rapid antibody test which samples oral/salivary fluid and avoids the need for phlebotomy. According to a field study, the sensitivity of the test was 97.8% and specificity 100% (53).

Individuals attending participating services in the four sites (Dublin, London, Bucharest, Seville) will be offered HCV screening using the OraQuick test. Those who accept the screening offer and test antibody positive (Ab+), and individuals who indicate they have already been diagnosed with HCV but have not received or engaged with specialist follow-up, will be offered further evaluation for HCV, including: HCV polymerase chain reaction (PCR) and antigen test to determine whether they have chronic infection, FibroScan to assess the extent of liver disease, and referral for HCV treatment if eligible. Individuals once referred to specialist hepatology/infectious diseases services will be assessed as to their suitability for HCV treatment and any barriers to treatment will be identified. The original service from which participants were recruited, with the involvement of allied health professionals, can develop a care plan to address the issues preventing treatment. HepCheck will thus address engagement with HCV evaluation and treatment as well as screening, by using the POCT offer as the entry point into the cascade of care required to be cured of HCV.

A minimum of 2,000 individuals will be screened for HCV across the four sites. We will evaluate the feasibility, acceptability and potential efficacy of the screening interventions for individuals attending homeless and other services in the partner sites, including establishing

the utility of POCT with HCV oral tests in diverse populations and different countries/settings. A quantitative audit of access to HCV treatment and of treatment outcomes in HCV-infected individuals identified during the screening process will be conducted. Qualitative interviews with a purposive sample of participants will examine acceptability of the interventions and barriers and facilitators to HCV treatment completion.

2.3.2 HepLink

This WP will develop, implement and evaluate a complex intervention to improve linkage to HCV evaluation and treatment among OST patients attending general practice and specialised OST centers. In many EU countries, including Ireland, Spain and the UK, general practice is increasingly involved in providing OST and continuing care for PWID. It is thus a key setting to target to address HCV-related morbidity and mortality among PWID. In Romania, OST is not prescribed by GPs but is provided through specialised centers. GPs and other OST prescribers often have long-standing relationships with their OST patients and as such can facilitate access to HCV evaluation and treatment among PWID where shared care partnerships with secondary/tertiary providers are developed.

HepLink will outreach a HCV-trained liaison nurse into GP practices and OST centers to optimise interaction and integration between primary and secondary care. S/he will conduct on-site specialist evaluation of HCV disease (including FibroScan) in the general practice / OST center setting, and assist in referring HCV-infected patients to a hepatology/Infectious Diseases service for HCV treatment. S/he will educate OST providers, GPs, practice staff and patients on HCV and developments in its diagnosis and treatment and ensure that patients' HCV testing and other blood borne virus screening and vaccinations are up-to-date. Research

has shown that practitioner education and nurse liaison can increase rates of HCV screening and linkage to specialist care in general practice (54).

A central component of the intervention will be the staging of liver fibrosis among HCV-infected patients using a FibroScan. Studies have shown the FibroScan to be equivalent to liver biopsy, although obesity, female sex, operator experience, and age older than 52 may give invalid results (55, 56). Currently, in many HCV treatment guidelines, a FibroScan is used to determine eligibility for state-supported HCV treatment utilizing DAA therapies. Thus the FibroScan has become an essential component of the evaluation of patients with HCV.

Twenty-four OST-prescribing GP practices and OST centers and 240 patients will be recruited across the four participating sites. In addition to developing and delivering the complex intervention, we will evaluate the intervention's feasibility, acceptability and likely efficacy within the different countries / health systems. An audit of patients' clinical records will be conducted at baseline and 6-months post-intervention to examine HCV care processes and outcomes following the intervention. Qualitative interviews with a purposive sample of OST providers and patients will assess the intervention's acceptability.

2.3.3 HepFriend

This WP will develop and implement peer support interventions to enhance engagement with HCV screening, assessment and treatment within the HepCheck and HepLink WPs. Peers are individuals with similar life or disease experiences to the clients they are supporting, i.e. HCV infection / drug misuse / homelessness. We will recruit, train and support peers to

improve HCV care integration between community and specialist services following the development of the HepCheck and HepLink interventions.

Peers will be trained to assist the clinical teams in HepCheck and HepLink with POCT, FibroScanning, and conducting pre-treatment assessments. They will receive training in how to support people through the HCV cascade of care, including those who are eligible for or undergoing HCV treatment. Peers will support clients by giving advice and education around the care pathway, accompanying clients to clinical appointments if desired, reminding clients of appointments, and meeting clients for social support. HepFriend will be conducted at all four sites.

We will determine the feasibility, acceptability and potential efficacy of the peer support interventions combined with HepCheck and HepLink, to improve HCV case detection and treatment uptake and outcomes in the diverse populations and different countries/settings. The client and peer experience of peer support will be assessed by qualitative interviews.

2.3.4 HepEd

There have been a number of developments in HCV diagnostics and treatment in recent years. However, a cultural lag has been identified between such developments and societal understandings of them (57). This WP will develop and deliver educational interventions to prepare affected communities for HCV testing, assessment and treatment and to prepare healthcare providers to act as partners in a shared care primary/secondary partnership for treatment of HCV. These interventions will be utilised within the other WPs of the project, i.e. HepCheck, HepLink and HepFriend.

HepEd will:

- Develop and implement a programme of multidisciplinary, inter-professional education on HCV for healthcare providers. This will include the hosting of Masterclasses on HCV and advances in its diagnosis and treatment for a minimum of 30 healthcare providers at each of the four sites (i.e. 120 providers in total) and the development of video and online resources to reach a wider audience.
- Develop and/or adapt educational materials for use in affected communities, including PWIDs. This will include educational materials to prevent those who test negative from subsequently acquiring HCV.
- Develop and adapt training materials for peers (i.e. HepFriend).

To evaluate the impact of the HCV masterclasses, attendees will be asked to complete pre- and post-intervention questionnaires on their experience of the masterclass and the extent to which they found it of value in providing HCV care for patients.

2.3.5 HepCost

This WP will evaluate the cost-effectiveness of the various Hepcare interventions in the different countries / settings and use the results to help guide decision criteria for when specific case-finding and care strategies should be used. The four interventions to be evaluated are HepCheck, HepLink, HepFriend and HepEd.

An existing dynamic compartmental model of HCV disease progression, screening, treatment and transmission among PWID and non or ex-PWID will be adapted to evaluate the Hepcare interventions. The model will initially be parameterised to evaluate each intervention in a

specific setting, and then adapted to consider the other settings. One setting will be modelled as a base case for each intervention and then the other settings will be modelled as a sensitivity analysis based on that primary setting. We will perform extensive sensitivity analysis to explore thresholds of cost-effectiveness in terms of minimum levels of intervention effect or testing yield, as well as what key factors and changes to the intervention may increase or decrease cost-effectiveness.

2.3.6 Dissemination

This WP aims to maximise the dissemination of findings from the project and its impact on HCV policy and practice nationally and in Europe. In addition to disseminating findings to healthcare professionals, affected communities, and the scientific community through conferences, peer-reviewed publications and social media, we will proactively engage with key stakeholders and policy-makers, nationally and in the EU, including service-user organizations, NGOs, key people responsible for national HCV policy at each site, and EU HCV and drug policy agencies.

2.3.7 Evaluation

This WP will evaluate how the project is addressing its overarching objectives and will consist of an external review by an approved agency with experience in evaluating EU level grants, in addition to regular internal reviews by the Project Steering Group.

2.5 Data generation and outcome measures

Several key outcome measures relating to the cascade of HCV care pre- and post-intervention will be examined in all WPs and settings, including: number and proportion of participants tested for HCV infection; number and proportion who are HCV positive; number and

proportion of HCV-positive patients who are: FibroScanned; referred to specialist care; attended specialist care; initiated HCV treatment; completed HCV treatment; achieved SVR; and number and proportion of deaths. Data will be generated through review of patients' clinical records and through questionnaires and interviews with patients and healthcare providers.

To facilitate clinical and research follow-up of participants, individuals contact details as well as the contact details of their GP and other support services will be collected at recruitment to the study. Follow-up data on access to and retention in HCV care (e.g. engagement with specialist services, treatment completion etc) will be collected by the research team from the participants' health records and/or from follow-up questionnaires with participants. In the latter case, members of the research team will contact participants directly or via their support service/care team.

Data on participants alcohol and drug use will be collected as part of the HepCheck and HepLink WPs and will form part of the patient referral information that is forwarded to hepatology/infectious diseases services. Detailed data on previous and current drug use (including drugs used, mode of administration, and frequency of use) will be collected as part of HepCheck and will enable an analysis of the potential associations between psychoactive substances use and HCV treatment outcomes.

2.5.1 Health Economics

Cost-effectiveness results will be expressed in terms of incremental cost of effectiveness ratios (ICERS) for each of the interventions, country-specific. The costs for each intervention will be estimated for each country/setting, including staff time spent on the intervention and

any relevant training and equipment costs. Treatment and care costs will be estimated following discussions with health care providers in each setting, and applying or adapting available costs from their or other EU settings. This will include costs for individuals that commence HCV treatment and those that do not. Health care benefits will be estimated in terms of quality adjusted life years saved (QALYS) with existing health utility data being used for different HCV disease stages.

2.6 Ethical Considerations and Project Governance

Ethical approval for the project has been received from our respective institutional review boards in the four fieldwork settings (i.e. Mater Misericordiae University Hospital, Dublin; Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest; Hospital Universitario de Valme, Seville; North West - Haydock Research Ethics Committee, London).

The project governance structure includes: (i) an International Advisory Board, composed of academics, clinicians, researchers, and representatives from relevant EU regulatory bodies and service-user organisations, to provide external oversight; (ii) a Project Steering Group, composed of WP leaders and site leaders, to provide internal oversight; and (iii) site-specific Project Management Teams to execute the project at each site.

3. DISCUSSION

We have described the focus of the Hepcare Europe project which is to develop, implement and evaluate interventions to enhance diagnosis, evaluation and treatment of HCV among PWID. PWID at risk of or infected with HCV often have complex needs. Many are unaware of their infection and those diagnosed often do not access specialist care. Recent

developments making HCV testing and evaluation more portable, less invasive and less reliant on specialists, enhance opportunities for further extension of HCV care to community settings to reach more patients. Hepcare Europe will design and evaluate outreach interventions to PWID and linked groups such as the homeless, through their points of contact with services in the community, e.g. prison, addiction services, primary care, hostels, and NGOs, in four European sites. Interventions will focus on enhancing HCV testing and evaluation of HCV disease in the community through education, point-of-care diagnostics, nurse outreach, and peer support, and will create shared care partnerships between secondary/tertiary and primary/community care to facilitate diagnosed patients to access treatment with the recently available DAAs. We will evaluate the feasibility, acceptability, potential efficacy, and cost-effectiveness of the interventions to improve HCV care processes and outcomes for PWID in a variety of settings in the four sites.

While the Hepcare package of interventions aim to facilitate access to HCV treatment, the interventions will not change treatment eligibility criteria/recommendations. Decisions regarding HCV treatment of individual participants (i.e. treatment eligibility and treatment regimen) will be made by clinicians within the specialist hepatology/infectious diseases services to which HCV-infected participants are referred, and will be based on each region/country's own national guidelines and policies.

We have created a consortium of researchers and clinicians active in HCV care in Ireland, UK, Spain and Romania to support mutual learning and implementation of interventions across sites. The geography and history of the sites reflect the epidemiological and demographic diversity in risk populations and diversity in socio-economic and political environments across Europe. Sites vary in the structure of their health systems, models of

primary care, and policies around OST provision, harm reduction and access to the new DAA therapies. The UK, for example, has a well-developed social welfare programme and free health care through the National Health System. Ireland has a different model of care, with private and public health provision. Spain similarly has a private/public partnership in the provision of medical care and economic restrictions at present on its health care budget. Romania, as one of the newer members of the EU, still has some barriers in its systems of care. The logistics of developing integrated models of HCV care will differ across sites given their heterogeneity. Through our work and partnership, we will interrogate the issues, from testing to treatment, to implement new models of care that are adapted to the needs of PWID.

To our knowledge, Hepcare Europe is the first multi-country European feasibility study examining interventions targeting all points in the HCV cascade of care from case-finding to treatment in diverse populations of PWID in a range of settings and countries. Other initiatives, such as The Extension for Community Healthcare Outcomes (ECHO) project (25, 58), The Enhancing Treatment for Hepatitis C in Opioid Substitution Settings (ETHOS) study (23, 26), The Hepatitis C Assessment and Testing (HepCAT) project (59-61), and The Hepatitis C: Assessment through to Treatment (HepCATT) study (62, 63), and more recent studies in the Netherlands (64), Ukraine (65) and Scotland (66) are based in single countries or outside Europe, are focused on particular points in the HCV cascade of care (e.g. testing and referral or evaluation and treatment), and do not include the broad range of settings that Hepcare will. We hope that Hepcare with its breadth and scope will complement these more focused studies.

3.1 Methodological considerations

As a pre-post feasibility study using mixed methods (mathematical modelling, qualitative data, cross-sectional, and longitudinal cohort elements), Hepcare does not employ a controlled trial design and lacks the scientific rigour of a RCT which could definitively determine effectiveness of the interventions. Also, as Hepcare interventions will be tailored according to the service infrastructure and population needs at each site, the implementation of interventions will not be homogenous.

However, this is a real world service innovation project that aims to design and deliver interventions that will meet the needs of PWID populations in a variety of settings in four European sites. We have used the information gleaned from the literature and lessons learned from previous studies to generate a programme of work which we propose will deliver evidence-based interventions (i.e. POCT, FibroScan, nurse liaison) though means and modalities that will be convenient and adapted to the needs of PWID.

Analyses of the Hepcare data will indicate which components of the Hepcare package of interventions work well and which don't in different real world settings and populations. This will allow further refinement of the interventions. Cross-sectional analyses of the data will provide insights into the uptake of the interventions, while longitudinal data will provide information on the potential impact of the interventions over time, including the throughput of participants in the cascade of HCV care. Qualitative data will provide insights into the acceptability of the interventions to service-providers and service-users. Health economic analyses will indicate the cost-effectiveness of the interventions and how this may vary in different settings.

One possible threat to our study is the effect on efficacy outcome measures of the continuing evolution of national HCV treatment strategies and treatment eligibility criteria within each country, which will impact study outcome measures such as HCV treatment uptake and SVR, and may have knock-on effects on measures such as referral and attendance at specialist services. At the same time, this evolution provides opportunities for Hepcare Europe to influence the direction of national HCV strategies through its pro-active engagement with policy-makers.

3.2 Implications for research, education, practice and policy

As a service innovation project involving PWID populations in a variety of settings in four European sites, lessons learned from the project will provide real world contributions to implementation science regarding community-based interventions for HCV infection among PWID and linked groups. This may also inform the design of subsequent RCTs in this area. The findings from this feasibility study may inform integrated care research more broadly, particularly for marginalised groups.

The interventions being developed as part of Hepcare have the potential to make an important impact on patient care through providing quality healthcare to marginalised populations who might otherwise go undiagnosed and untreated.

The development of online educational materials will create a continuing resource for patients and healthcare professionals across Europe and may inform educational interventions for the aforementioned groups, in particular ensuring these are applicable for an international audience.

Lessons learned from the study can be incorporated into national and European guidelines and strategies for HCV. Consortium members are actively engaged with key stakeholders and policy-makers locally and nationally to ensure that Hepcare addresses key issues in their region/country and contributes to improved policy and practice. Preliminary learnings from the project have already informed national HCV screening guidelines in Ireland (35).

3.3 Conclusions

HCV infection is highly prevalent among PWID. Yet many PWID are unaware of their infection and few have received HCV treatment. The burden of HCV-related liver disease is growing and is expected to increase substantially in the next decade. The potential of the new HCV therapies to address this burden and to achieve the reductions in HCV-related mortality set out in the WHO GHSS will only be realised if the identification of HCV among PWID and linkage to care and treatment of those who are chronically infected is optimised.

Taken together, our research findings will determine the feasibility, acceptability, likely efficacy, and cost-effectiveness of new models of care for engaging and retaining PWID in the cascade of HCV care. The analyses conducted as part of Hepcare Europe will be key in highlighting evidence for a scaled-up integrated care strategy for HCV infection in participating countries and in Europe.

Key Issues

- Hepatitis C (HCV) infection is associated with liver cirrhosis and hepatocellular carcinoma, and is highly prevalent among people who inject drugs (PWID).
- Many PWID are unaware of their infection and few have received HCV treatment.

- The burden of HCV-related liver disease among PWID will substantially increase in the next decade.
- Developments in HCV treatment have increased cure rates to >90%, in addition to shortening treatment times and improving safety profiles.
- As many PWID remain unaware of their infection and/or are not accessing HCV care, it is evident that new strategies to reach such individuals are necessary, including new testing strategies to increase the number diagnosed, and improved care pathways to ensure those diagnosed are successfully linked to HCV evaluation and treatment.
- Hepcare Europe is an EU-supported, service innovation project, involving collaboration between five institutions across four member states (Ireland, UK, Spain, Romania). The project aims to develop, implement and evaluate interventions to improve HCV identification, evaluation and treatment among PWID and linked groups such as the homeless and prisoners through their points of contact with services in the community in Dublin, London, Seville and Bucharest.
- The geography and history of the four sites reflect the epidemiological and demographic diversity in risk populations and diversity in socio-economic and political environments across Europe.
- Interventions will be tailored to the health service infrastructure and population needs at each site and will incorporate point-of-care-diagnostics, nurse outreach, community-based evaluation of HCV disease, health provider and patient education, peer support, and the development of integrated models of HCV care.
- We will evaluate the feasibility, acceptability, potential efficacy and cost-effectiveness of these interventions to get a better understanding of how improvements to the care of PWID can be achieved.

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Table 1: HCV infection in the general population, PWID population and coverage of harm reduction measures in Hepcare Europe countries

Countries	CHC in general population	HCV prevalence among PWID	OST: Forms provided	[a]OST: Coverage*	[a]NSP: Coverage[†]
Ireland	20,000-30,000	62-81%	Methadone	High: GTP (93-GTP)	Low: 46 (37-62)
UK	214,000	52%	Methadone, Buprenorphine, Diamorphine	England High: 67 (62-72) Scotland Moderate: 23 (21-27) Wales: NC Northern Ireland: NC	England: NE Scotland High: 277 (249-321) Wales: NC Northern Ireland: NC
Romania	489,000	82.4%	Methadone, Buprenorphine, Combination Buprenorphine/ Naloxone	Low: 1 (<1-1)	Low: 18 (13-24)
Spain	472,000	60-80%	Methadone, Combination Buprenorphine/ Naloxone	High: GTP	Moderate:141 (84-428)

CHC: Chronic Hepatitis C; HCV: Hepatitis C Virus; OST: Opioid Substitution Treatment; NSP: Needle and syringe programmes; GTP – estimate greater than parity; NC: intervention exists and data on the extent of service provision were identified for this country, but no estimate of the prevalence of injecting drug use has been located for this country;
NE: intervention exists in that country, but no data on the extent of service provision were located;
*Number of OST clients per 100 PWID; [†]Number of needle-syringes distributed per PWID per year
a (Larney, Peacock et al. 2017) (46)

Figure 1: Hepcare Europe Work Packages

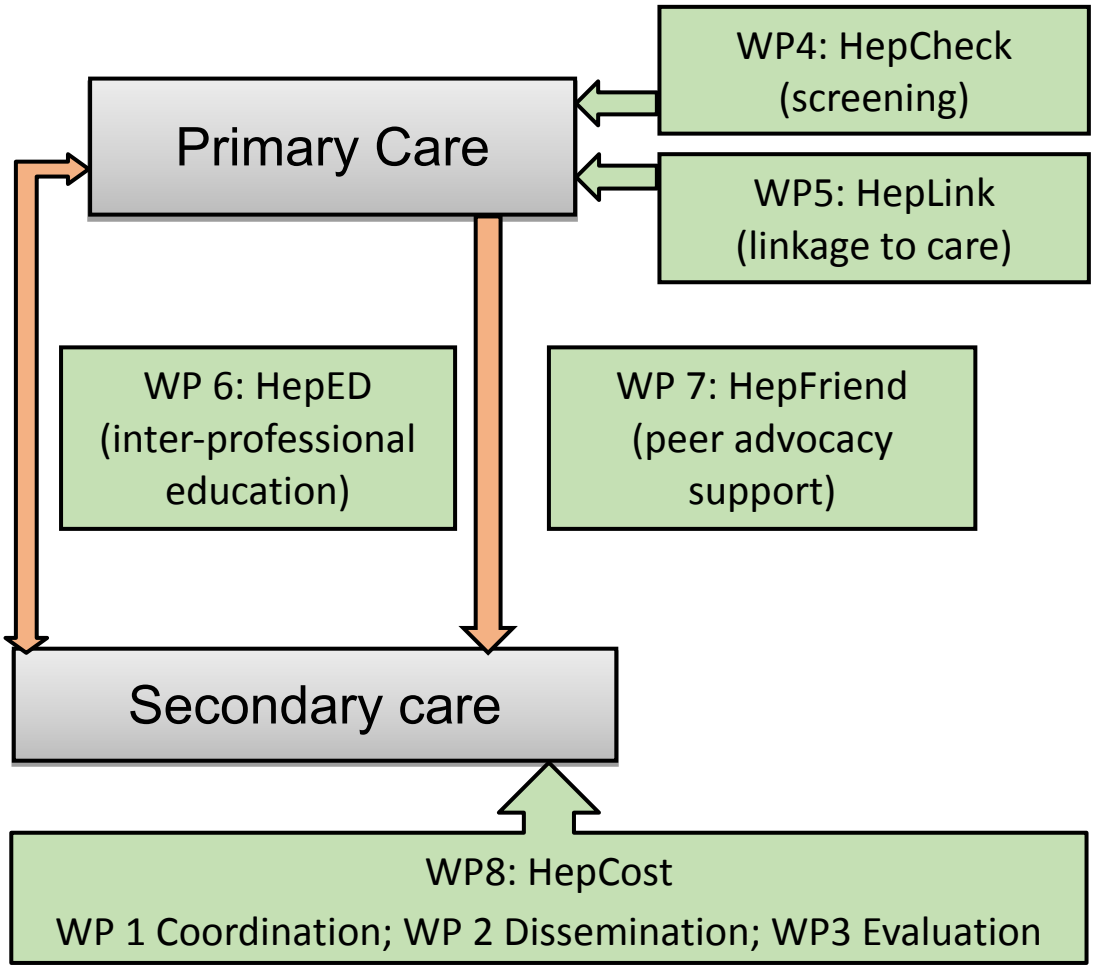

Table 2: Hepcare Europe Work Packages: Study populations, interventions, comparisons and key outcomes (PICO)

Work Package	Population	Intervention	Comparison	Outcomes
HepCheck	• Prisoners (Dublin) • Homeless; PWID (Bucharest) • Underserved communities (London) • Homeless; PWUD (Spain) (Target: screening 2000 individuals at-risk of HCV across 4 participating sites)	Outreach and point of care testing of at-risk populations	Pre-post intervention	N individuals screened for HCV N new cases of HCV detected N HCV-positive participants: • FibroScanned • Referred to hepatology/ID • Attended hepatology/ID • Started HCV treatment • Completed HCV treatment • Attained SVR
HepLink	• Patients on OST in GP practices / OST Centers Target : 24 practices/centers and 240 patients across 4 participating sites	Outreach of a HCV-trained nurse into GP practices/OST centers to provide HCV education, community-based evaluation of HCV disease, and assist with referral to specialist care	Pre-post intervention	N participants screened for HCV N participants HCV positive N HCV-positive participants: • FibroScanned • Referred to hepatology/ID • Attended hepatology/ID • Started HCV treatment • Completed HCV treatment • Attained SVR

HepEd	• Healthcare professionals (all sites) • Patients (all sites) • Peers (all sites)	Development of educational resources for health care providers, patients and peers	Pre-post masterclass survey	Improvements in HCV knowledge
HepFriend	• Underserved communities (London) • Patients on OST/PWID (Seville) • Prisoners (Dublin) • Homeless (Bucharest)	Peer support system to assist at-risk groups to engage with screening, assessment and treatment within HepCheck and HepLink	Pre-post intervention	N participants screened for HCV N HCV-positive participants: • FibroScanned • Referred to hepatology/ID • Attended hepatology/ID • Started HCV treatment • Completed HCV treatment • Attained SVR

PWID: People who inject drugs; PWUD: People who use drugs; HCV: Hepatitis C Virus; ID: Infectious Diseases; SVR: Sustained Virologic Response