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Developing a Community HCV Service: Project ITTREAT (Integrated Community based Test - stage - TREAT) Service for People who Inject Drugs

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Running title: A new community HCV Model (ITTREAT)

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Abstract

Liver disease is now the third most common cause of premature death in the UK, with chronic viral hepatitis being an important contributory factor. Often the diagnosis of chronic liver disease is only made when patients present late in the disease trajectory. This underscores the importance of near patient testing and linkage into care. The need for community based models for liver disease is in line with the recently commissioned National Liver report, which calls for assessment and treatment of high-risk individuals in the community.

In this manuscript our objectives are to discuss the need for community services for individuals with hepatitis C virus (HCV) infection and give an overview of the different community models for HCV. Finally we describe our experiences in setting up a successful nurse led service for screening, stratification and treatment of HCV related liver disease at a substance misuse service. We highlight the important stages of this process including engaging with stakeholders, obtaining funding and service set up. We also explore the obstacles and challenges faced and summarise our key recommendations. A brief summary of interim clinical outcomes is also presented.

Key words: HCV, HEPATITIS C, CLD, COMMUNITY MODEL, PWID

Background and aims

Liver disease is the third most common cause of premature death in the UK (Williams et al., 2014). Chronic hepatitis C virus (HCV) infection remains a major national health burden (HCV in England 2017 report, 2017) with an estimated 160,000 individuals infected (Harris et al., 2012). Globally, deaths from viral hepatitis (1.4 million/yr) have now surpassed that of HIV (1.3 million/yr), and malaria (1.2 million/yr) and TB (0.5 million/yr) combined (Global Burden of Disease and WHO/UNAIDS estimates.; 2015). This mandated the first ever WHO Global Health Sector Strategy (GHSS) in May 2016, which aims for elimination of viral hepatitis by 2030 (WHO, 2016). The vision statement of Public Health England (PHE) 2017 Hepatitis C report is in line with the WHO GHSS (HCV in England 2017 report, 2017).

Injecting drug use is responsible for 90% of all HCV infections in England (HCV in England 2017 report, 2017), with 52% of people who inject drugs (PWID) having a positive HCV serology (PHE HCV in England 2017 Headline data table, 2017). PHE estimates that about 50% of individuals with HCV may have already been diagnosed (HCV in England 2017 report, 2017), however only 53% PWID sampled are aware of their HCV antibody positivity status (People who inject drugs UAMS Survey, 2017).

Due to the advent of direct acting antivirals (DAAs), there has been a paradigm shift in the management of chronic HCV infection. DAAs have sustained virological response (SVR) rates (i.e. cure) in the high 90% despite shorter durations of treatment (on average 12 weeks), and are effective orally (Bell et al., 2016; Feld et al., 2014; Feld et al., 2015; Kowdley et al., 2014). In England, From June 2015-April 2016,

38% more individuals (7,036) accessed treatment (Interim Clinical Commissioning Policy Statement, 2014 and Clinical Commissioning Policy Statement, 2015) than mean 2008-2014 levels (PHE HCV in England 2017 report, 2017). This may have contributed to the 8% reduction in deaths from HCV related ESLD and HCC (PHE HCV in England 2017 report, 2017) and 38% reduction in liver transplantation (38%) in 2015 (UK Transplant Registry, 2017). DAA treatment outcomes in PWID are comparable to those in secondary care (Dore et al., 2016).

Despite the discovery of DAAs however, we still need a three-five-fold increase in HCV diagnosis and treatment if we are to stem the national HCV burden (Wedemeyer et al., 2014). However, PWID remain a vulnerable cohort with poor engagement with hospital services

The objectives of this manuscript are to present the need for community HCV services for PWID, give an overview of the different community models for HCV and finally describe our experiences in setting up a successful nurse led HCV service at a substance misuse service (SMS). Detailed outcome data will not be presented in this manuscript as final data analysis (clinical, qualitative, patient reported and health economic outcomes) will be completed mid 2018 and with the aim to publish in a Hepatology focussed journal. However, a brief summary of interim clinical outcomes is provided.

HCV community service development

Stage 1: Establishing a need

Economic modeling suggests that prioritizing HCV treatment in PWID with a $\leq 40\%$ HCV seroprevalence and mild to moderate liver disease (in combination with opioid

substitution therapy (OST)/needle and syringe programs) is more cost-effective than treating other patient groups because of the additional benefit of avoiding onwards transmission also known as “treatment as prevention” (Martin et al., 2013; Martin et al., 2016).

An earlier study from Nottingham however showed that overall only 49% of individuals with a positive HCV serology were referred to a specialist, 27% attended and 10% were treated (Irving et al.; 2006). A re audit about 10 years later showed improvement (80% referred, 70% attended and 38% commenced treatment) though clearly there remained scope for improvement (Howes et al.; 2016). Barriers to HCV treatment remain at all levels of care (patient, provider and national) (see Fig 1). These include the complex nature of HCV treatment (until recently), inability of health care providers to appreciate the complex needs of vulnerable PWID, perceived stigmatisation and reluctance to treat those actively engaged in alcohol and substance misuse (Irving et al.; 2006, Marufu et al., 2011; Dillon.; 2016).

Locally and as reported by others (Mehta et al., 2008; Lewis et al., 2016) we have been cognisant of the poor uptake of HCV services by PWID. In 2011 we appointed a hepatitis nurse at the largest SMS in Brighton to perform blood dry blood spot testing (DBST) for blood borne virus (BBV) screening with onward referral to Hepatology services. Over a six-month period, of those identified with a positive BBV screen (n=73), 14 (19.1%) were known to Hepatology services (two previously treated). Of the forty individuals suitable for antiviral treatment, only two (5%) engaged with secondary care (42% declined a referral and 37% disengagement with SMS). No individual was eventually treated (Marufu et al., 2012). Poor uptake of HCV treatment may be contributing to Brighton and Hove having the highest hospital

admission /100,000 population with HCV related end stage liver disease (ESLD) and hepatocellular cancer (HCC) (4.8, 95% CI 3.4-6.5), and highest mortality in those aged < 75yrs from HCV related ESLD and HCC (1.39, 95% CI 0.70-2.49) in the south east (PHE fingertips).

These data indicates the value of developing innovative community HCV services. Such a novel strategy would represent patient-centred care with earlier diagnosis and treatment, prevention of onwards-viral transmission and potential for reduction in health inequalities. A community-based model with linkage to care is in line with the recently commissioned National Liver Report that advocates screening and treatment for chronic liver disease in the community (Williams et al., 2014).

NHS targets are to treat 10,000 individuals with HCV infection in 2016, increasing to 15,000/year in 2020 (PHE HCV in England report, 2017). If achieved, statistical modelling predicts that around 2620 people would be living with HCV-related cirrhosis or HCC (a 81% reduction) in England by 2030 (Harris et al., 2016) as mandated by the WHO (WHO, 2016). This is however unlikely to be achieved without engaging PWID.

2. Overview of HCV community models of care

The model of specialist hepatitis nurses working in SMS/drug and alcohol services has been implemented before, though care has been fragmented, with BBV screening at SMS followed by referral to secondary care (Marufu et al., 2012); Even if nurse led treatment has been provided at SMS it is often delivered via out-reach intermittent clinics (Selvapatt et al., 2016) and does not always include assessment of hepatic

fibrosis (Grebely et al., 2016). In other models, homeless individuals attending addiction centres underwent review by a consultant Hepatologist and a hepatitis nurse but again only on an intermittent (monthly) basis (Wilkinson et al., 2009). Directly Observed Therapy (DOT) with pegylated interferon (peg-IFN) and ribavirin (RBV) have also been incorporated into opioid substitution clinics (Bonkovsky et al., 2008). Nonetheless, these DOT models are limited to small randomised controlled trials and involve close collaboration with secondary and tertiary services- not always feasible in a community setting (Bruggmann & Litwin, 2013).

Group or peer based treatment has also been trialled, in which an experienced peer co leads the treatment along with a medical provider. This has led to successful treatment outcomes in various settings but relies on pre-treatment engagement (Sylvestre & Clements, 2007). In addition, this model is dependent on excellent group dynamics and effective communication between the peers (Bruggmann & Litwin, 2013).

In the General Practitioner (GP) based model, a GP with additional HCV training offers treatment to PWIDs alongside OST (Seidenberg et al., 2013). While this model is simple, provision of addiction and HCV treatment by a single GP is demanding and requires great commitment, effort and training of the primary care provider (Seidenberg et al., 2013). Other primary care strategies employed a specialist nurse working in general practices (Jack et al., 2009), but many PWIDs do not engage with their GPs. The Australians however have managed to treat > 20,000 individuals with HCV infection during Mar-Jun 2016 (previously 2,000-3,000 patients treated per/yr). Multiple factors contributed to this phenomenal success including prescribing by GPs (Kirby Institute, Australia, 2016). In a recent on-going study in South West England, patients in 46 general practices are being randomised to receive either standard care or

a complex intervention comprising educational training, posters and leaflets display, the aim being to raise awareness and encourage opportunistic testing through risk prediction algorithms (Roberts et al., 2016).

Other established community HCV programmes such as the American ECHO (The Extension for Community Healthcare Outcomes) project have also shown great success (Arora et al., 2010). This model links Hepatologists with primary care physicians in local communities via telehealth technology. It allows optimal management of HCV patients through “knowledge networks,” bringing together expert interdisciplinary specialists from the hospital and multiple community-based primary care practitioners (Arora et al., 2010). Similar outcomes have also been shown in the Veteran Affairs –ECHO programme (Beste et al., 2016). Other innovative strategies include the French mobile hepatitis team (Remy et al., 2016). Table 1 summarises the pros and cons of the different community HCV models

Stage 2: Obtaining funding and assembling team

Having identified a clear unmet need to link PWID into care by developing a community HCV service model, we then engaged with various stakeholders [SMS, psychiatrists, patient groups (Hepatitis C Trust, British Liver Trust), Brighton and Hove Commissioners, and Pharma].

Our aim was to set up a unique “one-stop” HCV community clinic that provided all components of care (BBV screening, stratification of hepatic fibrosis, nurse-led HCV treatment under Hepatologist supervision, hepatitis B vaccination, OST and social and psychiatric input) at one site. In view of the complex needs of PWID our philosophy was that an integrated and multidisciplinary model based at a SMS had the best

chance of success. We selected this model rather than one based in primary care due to

- Our prior established links with the SMS enabling us to engage PWID in an environment they were comfortable in
- A recent meta-analysis identifying “treatment of addiction during HCV therapy” as a factor associated with higher treatment completion (Dimova et al., 2012)
- A historical reluctance by GPs in England to be involved in antiviral prescription.

In 2013, we obtained funding for two years (National Gilead Fellowship and Brighton and Hove Commissioners) to set up our community hepatitis C service at the SMS in Brighton (Sussex Partnership Trust). In 2015 additional funding from the same sources extended our work for two years (until Dec 2017). The funding allowed for appointment of a band 7-community hepatitis nurse and a health economics and qualitative researcher, mobile fibroscan purchase and data collection (clinical, qualitative, patient reported and health economic outcomes). The Fibroscan (fig 2) is a non-invasive painless liver scan that utilises liver stiffness as a measurement of severity of liver fibrosis (Sandrin et al., 2003). It is now a validated technique (sensitivity and specificity 80~90%) for detection of all stages of liver fibrosis in individuals with most aetiologies of chronic liver disease including HCV (Sandrin et al., 2003; Talwalkar et al., 2007).

Stage 3: Service set up

This involved training of the hepatitis nurse (MOS), identification of a lead psychiatrist at the SMS (HW), and detailed discussions with managers at SMS to address logistic issues including clinic space. The service was publicised by the on-going engagement with stakeholders, MOS engaging with SMS staff and use of posters. In addition, both MOS and SV attended the monthly Substance Misuse Board, chaired by the Commissioners and usually well attended by various stakeholders. Fig 3 summarises the stages in setting up the community HCV service.

Prerequisites for a successful HCV community service

In our view the following were prerequisites for a successful HCV community service:

- An integrated and multidisciplinary approach with provision of all components of the service at one site, preferably a SMS
- An experienced community hepatitis nurse additionally trained in substance misuse and passionate about working with this client group to provide holistic care
- Easy access to nurse (mobile phone) and close supervision by a Hepatologist
- Flexible clinic appointments in contrast to the inflexible, non-personalised and stigmatised environment in secondary care.
- Community Fibroscan for non-invasive staging of hepatic fibrosis
- Presence of onsite psychiatrist
- On going alcohol and drug use not a bar to HCV treatment
- Personalised strategies for drug delivery (e.g. home delivery)

- Provision of peer advocates (buddies) to support clients throughout their treatment journey.
- Good engagement between key workers, drug and alcohol team, psychiatrist, peer advocates and hepatitis nurse.
- Non judgemental approach

The role of the hepatitis nurse is summarised in Fig 4 and participant pathway in Fig.

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4. Delivery logistics and barriers to success

Though the need for a community service was greatly appreciated, set up was associated with a variety of issues that included

- Scepticism “ it ain’t going to work”
- Concerns about treating those with on-going drug and alcohol use “can’t be trusted with expensive drugs”
- Misconceptions about treatment efficacy and reinfection risks in PWID
- Logistic issues especially lack of clinical space. Not infrequently clinical space had to be shared with the consultant psychiatrist. A change in providers in 2015 (Surrey and Borders) meant relocating the service to new premises. This heightened the issues of availability of clinical rooms, and there are on-going negotiations with management and clinical staff to resolve this problem.
- Concerns that interactions between the community hepatitis nurse, psychiatrist, and key workers would be incongruent.
- Remote access to hospital pathology and radiology database - this was resolved with the use of a laptop and remote modem.

- On-going need to train the staff at the SMS in BBV testing and providing them with the latest HCV treatment updates. This required not only regular training of the substance misuse teams but also reaching out to the wider community to include volunteers, peer mentors, those running Narcotics/Alcohol Anonymous meetings, homeless hostel workers, rehabilitation units staff and GP's. We are now in fact part of the GP rotation-teaching programme and provide update sessions to GPs on a regular basis highlighting the changes in HCV treatment and the criteria for referral to our service. In the past PWID would have been denied HCV treatment and so it is essential to dispel this antiquated myth amongst the medical and the wider community.
- Restrictive access to DAA due to prohibitive costs. The Early Access Programme (EAP) enabled treatment of those with decompensated cirrhosis due to a high probability of death and or irreversible damage within a year (Interim Clinical Commissioning Policy Statement, 2014). NHS England then extended treatment to cirrhotics (Clinical Commissioning Policy Statement, 2015) and subsequently to those with advanced fibrosis (LSM > 9.5 kPa). There are however exceptional criteria to include those with extra hepatic disease and PWID (as window of opportunity). Treatment can only be dispensed through nationally selected ODNs (n=22), of which we are one. Each patient is discussed at a weekly multidisciplinary meeting (MDM). Each genotype has a first choice regimen and all second choice drugs (which in fact maybe more appropriate) need "buddy ODN" approval. There are severe financial penalties for the ODN if guidelines are breached. Each ODN has been provided with a run rate based on the regional prevalence of HCV and

again, there are financial penalties for exceeding this. While each ODN can treat a subset of patients (10-20%) under the exceptional criteria, this remains highly scrutinised. It is therefore frustrating that despite effective antivirals and engaged SMS clients who often only have a small window of opportunity; we are still unable to offer treatment to a substantial number of PWID. This is in sharp contrast to countries like Australia where there is unrestricted access to DAA (including for re-infection) and primary care physicians are encouraged to take on prescribing and treatment as already stated (Kirby Institute, Australia, 2016). We have now initiated discussions to incentivise ODN that develop community out-reach programmes (for e.g. increased run rates).

- Need for upfront funding for service set up – this has somewhat been negated by establishment of ODN and availability of CQUIN funds

5. Evaluating the service

We aimed to evaluate this community based HCV service through collection of following data:

1. Clinical: demographics, drug and alcohol use, uptake of DBST, HBV vaccination and HCV treatment as well as treatment outcomes
2. Qualitative: Conduct of interviews with SMS attendees and two focus groups with staff members
3. Patient reported outcomes using validated questionnaires
 - a. Liver related quality of life (QOL) - Short-form Liver Disease Quality of Life (SF-LDQOL) (LDQOL; Kanwal et al., 2008)
 - b. Non-disease specific health related outcomes - SF-12v2, which is a shortened form (12 items) of the SF-36v2 Health Survey (SF-36)

4. Assessment of quality adjusted life years (QALY) using EQ-5D-5L (EQ-5D-5L survey) and perform a health economics (HE) assessment (cost per cure)

6. Progress

As already stated, detailed outcome data will not be presented in this manuscript. Our year 3 interim clinical outcomes have been selected for presentation at the American Association for Study of Liver Disease meeting (2017) and these are summarised below.

- To date, 485 individuals have been recruited, 80% (n=388) males, mean age 41.0 ± 9.9 yrs.
- Prevalence of injecting drug use (IDU) [336 (69%)], alcohol use [416 (86%)] and psychiatric illness [225(47%)] remains high.
- Uptake of DBST was 97% (n=472). Prevalence of positive serological markers/PCR were: HBcAb 20% (n=88), HCV antibody 56% (n=262) and HCV PCR 81% (211/262); genotypes 1=92 (44%) and 3= 94 (44%)
- Independent predictors of a positive HCV serology were age, if ever injected, positive HBcAb and if ever had a psychiatric diagnosis (p value for all ≤ 0.003).
- Of those with a positive HCV PCR (n=211), 169 (80%) underwent transient elastography (TE) [median liver stiffness measurement (LSM) 6.8 kPa (2.7-75), 76 (45%) having significant fibrosis (LSM ≥ 7.5 kPa, with 42 (25%) having cirrhosis.
- Sixty-six (31%) individuals were not treatment candidates (chaotic lifestyle), 87/145 (60%) of the remaining with a positive PCR commencing HCV treatment in the community.

- Characteristics of treated cohort were: age 46 ± 9.2 yrs; 84% male; 29% and 20% having on going alcohol and IDU respectively; 95% undergoing TE [median LSM 8.7 kPa (2.7-75), 39% (34) having cirrhosis including four with decompensation];
- Genotypes 1 = 48%, 3= 45%
- Treatment received: INF/RBV 18%, INF+DAA 21% and DAA 61%
- Treatment outcomes were: sustained virological response (SVR12) (47, 54%), end of treatment response (EOTR) awaiting SVR12 (12, 14%), nonresponse (NR) (4, 4%), responder relapse (RR) (5, 6%), and on going treatment (19, 22%). All but one NR/RR received INF based treatment
- Compliance with treatment was 97%
- No reinfection till date (O'Sullivan et al., 2017)

Project ITTREAT has also been presented at earlier national and international conferences (O'Sullivan et al., 2015; O'Sullivan et al., 2016; O'Sullivan et al., 2016) and was selected by PHE as a showcase for good clinical practice (HCV Action and PHE Hepatitis C Roadshow), 2015). Currently our managers are drafting a business case to allocate CQIN funds for permanency of the community hepatitis nurse post once funding runs out end of 2017. We are also exploring extension of the community hepatitis nurse role to include management of individuals with other forms of chronic liver disease including those with cirrhosis.

Based upon the success of Project ITTREAT our team has now established the VALID (Vulnerable Aadult Liver Disease) project. This is a similar integrated community liver service based at two homeless hostels and offers non-invasive

assessment of hepatic fibrosis (Fibroscan) followed by targeted treatment for chronic liver disease including for BBV (Hashim et al., 2016). NHS England have selected the VALID study for inclusion on a website which is a showcase for good practice (Learning Environment – NHS England, 2016).

Conclusions and the future

Linking PWIDs into care is essential if HCV infection is to be eliminated by 2030 as set out in the WHO strategy. These individuals have however consistently failed to access traditional models of secondary care. The advent of DAA provides an unprecedented opportunity to address the national HCV burden. Our integrated and multidisciplinary community models of care (Project ITTREAT, VALID Study) have been successful in engaging such individuals with outcomes comparable to secondary care, despite the complex nature of the cohort. Provision of all aspects of the care at one site, a dedicated and highly motivated team and the excellent communication between them and substance misuse staff, other community services, and stakeholders is the key to the success of this service. Our easy to replicate community HCV models have the potential for national adoption.

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Ethical approval was obtained (REC ref no 13/EM/0275)

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Table 1 Pros and cons of different community based HCV models of care

Community Model	Advantages	Limitations
Models based in General Practices. (Seidenberg et al., 2013; Jack et al., 2009)	Easy to establish and incorporates HCV and addiction treatment	Require extensive training of GPs
Directly Observed Treatment in substance misuse services (Bonkovsky et al., 2008)	Established evidence of enhanced adherence	Only small numbers can be achieved and often combined with secondary and tertiary referrals
Peer/group based treatment (Sylvestre & Clements, 2007)	Potentially improves compliance and enhances patient motivation.	Relies on positive pre-treatment engagement and group dynamics
Hepatitis specialist nurse in addiction units (Selvapatt et al., 2016; Wilkinson et al., 2009)	Offers specialist input with ability to screen and treat large numbers of patients.	Lacked of an integrated and multidisciplinary approach including non-invasive assessment of hepatic fibrosis
ECHO (Extension for Community Healthcare Outcomes) model (Arora et al., 2010; Beste et al., 2016)	Widely accepted and validated	Requires frequent networking between GPs and Hepatologists

Fig 1. Barriers to care in individuals with hepatitis C virus infection

Patient level

1. Majority are PWID with poor engagement with secondary care due to chaotic life style and competing priorities
2. Asymptomatic nature of the disease
3. Perceived stigmatisation and prior negative experiences with health services
4. Myths associated with antiviral treatment and liver biopsy

Provider level

1. Failure to understand complex needs of PWID
2. Lack of awareness, hence not a priority for health care professionals
3. Bureaucratic and inflexible hospital environment
4. Prejudice and reluctance to treat those with on going alcohol and drug use
5. Misconceptions regarding treatment efficacy and reinfection in PWID
6. Lack of multidisciplinary approach with suboptimal interactions between addiction specialists and Hepatologists

National level

1. Restricted access to antiviral drugs
2. Lack of accurate data on HCV epidemiology

Fig. 2 Portable *FibroScan*® 402 device

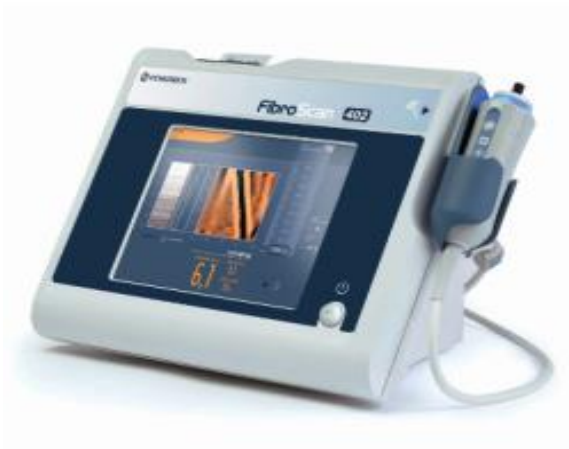
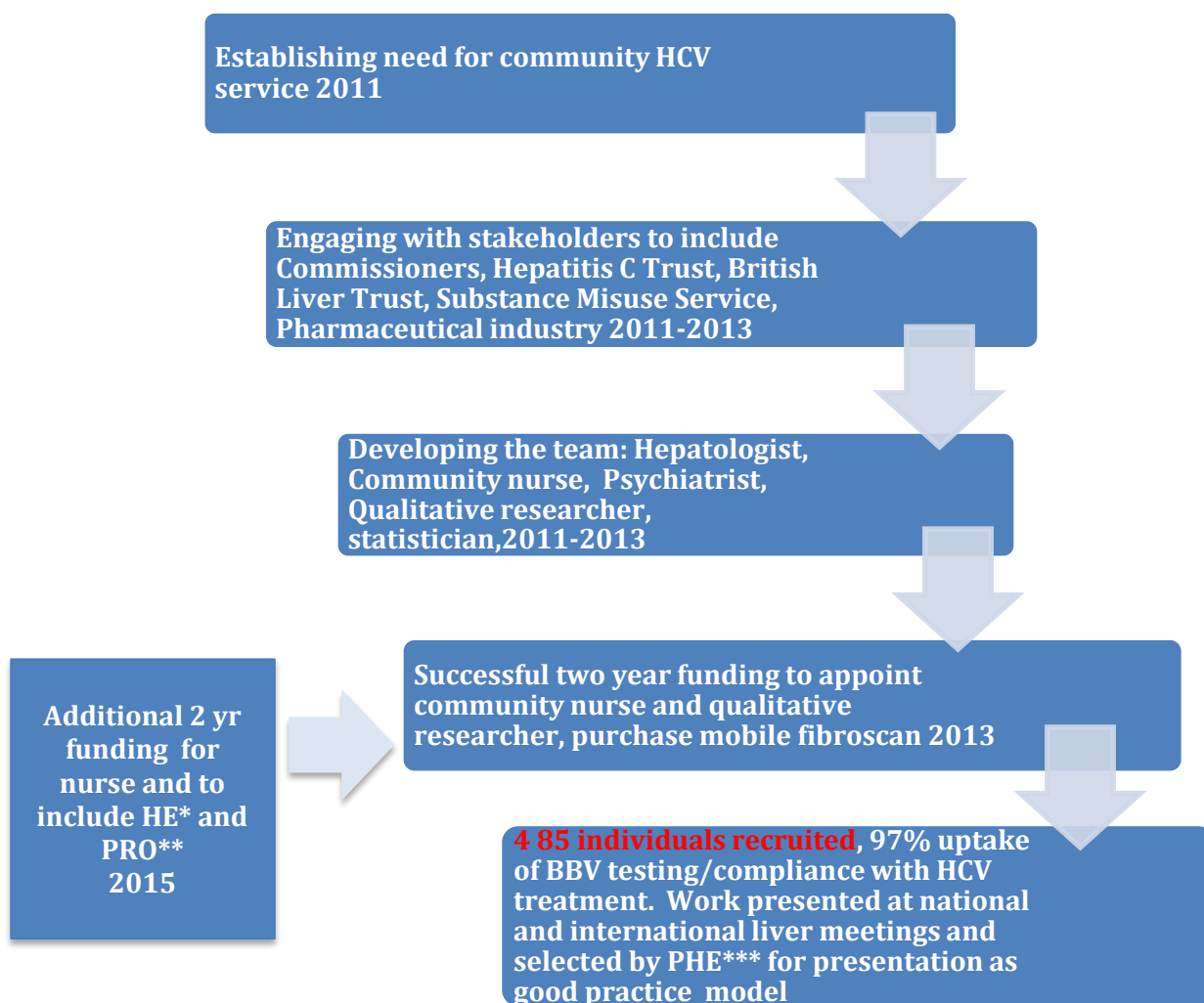


Fig 3 Stages in developing a community HCV service

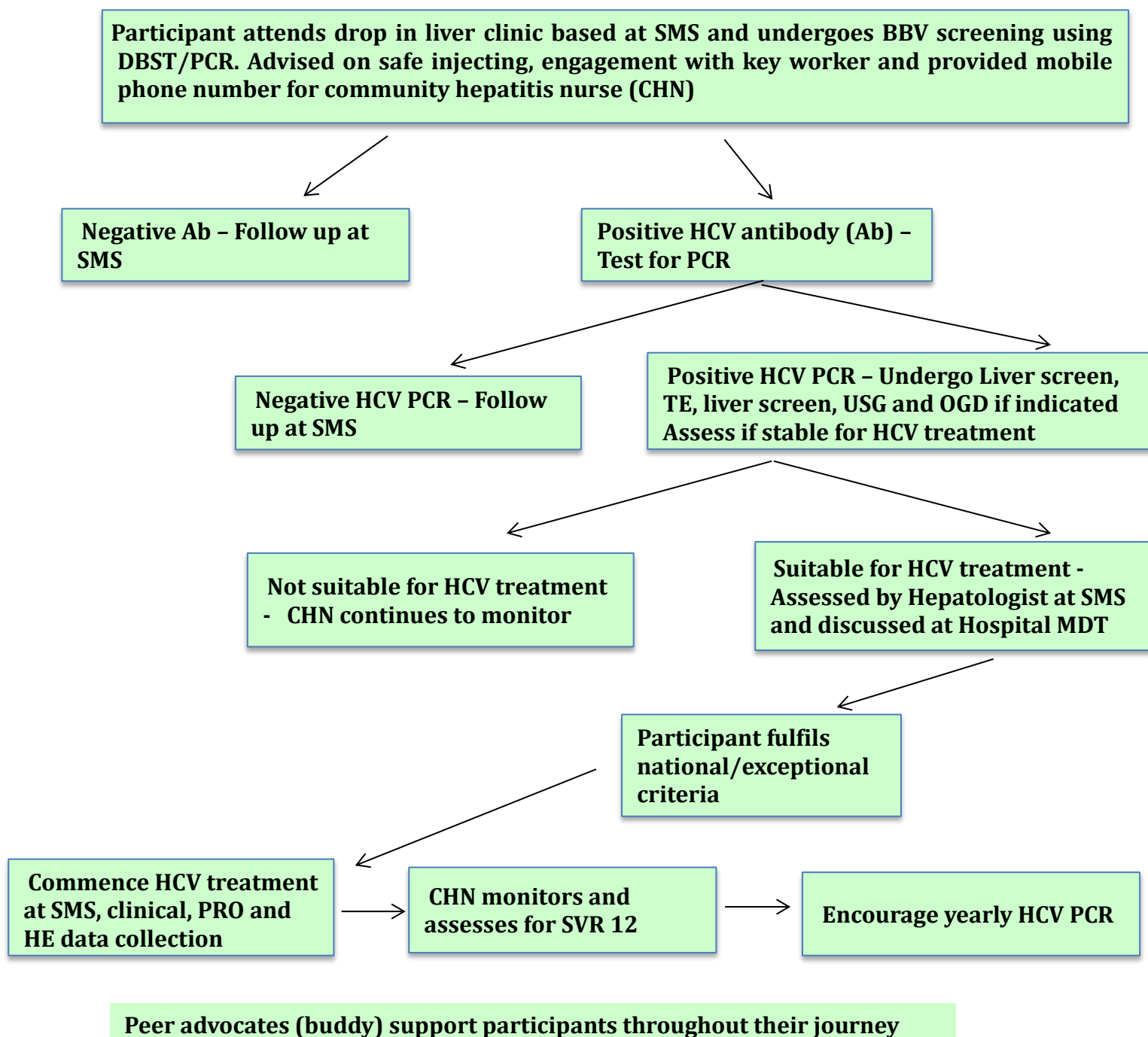


*HE = Health Economics
 **PRO = Patient Reported Outcomes
 ***PHE = Public Health England

Fig 4. Role of community hepatitis nurse

1. Testing for BBVs using DBST (dried blood spot testing), including confirmatory PCR for those who screen positive
2. Perform community based transient elastography for non-invasive assessment of hepatic fibrosis
3. Identify clients suitable for HCV treatment. Those with on going alcohol and substance misuse not excluded from treatment as long as willing to engage and stable housing.
4. Monitor HCV treatment under supervision of a Hepatologist.
5. Hepatitis B virus vaccination for those not immune
6. **Work** closely with psychiatrist, substance misuse counsellors, key workers **and peer advocates** to **ensure holistic care** including with social issues (housing etc)

Fig 5: Project ITTREAT: Participant pathway



SMS substance misuse service, BBV blood borne viruses; DBST direct blood spot testing, PCR polymerase chain reaction, TE transient elastography, USG ultrasound, OGD oesophagogastroduodenoscopy, PRO patient reported outcomes, HE health economics, SVR sustained virological response