Project Title:
Assessing the impact and cost-effectiveness of needle/syringe provision on hepatitis C transmission among people who inject drugs in the United Kingdom: analysis of pooled datasets and economic modelling.

1. Background

1.1. Existing research

Evidence shows that injecting with used needle/syringes and sharing injecting equipment is the main risk factor for infection with Hepatitis C and HIV among PWID.[1, 2] However, evaluation of interventions distributing needles/syringes remains woefully inadequate. While there is good evidence that needle and syringe programmes (NSP) and opiate substitution therapies (OST) in combination reduce injecting risk behaviours and some evidence to show the impact on HIV incidence, there is little evidence of their impact on hepatitis C (HCV) incidence among PWID. [3-7] Recently two reviews have estimated a moderate effect of NSPs on reducing HIV transmission by 48% (95% CI 3-72%) and strong evidence for OST reducing HIV transmission by 54% (95% CI 33-68%). [8, 9] Similar evidence is lacking for the effect of NSPs or OST on HCV. Previous reviews [7, 10, 11] have synthesised evidence for use of NSPs but focussed primarily on HIV as the main outcome and as a consequence failed to include all the available evidence on HCV. [5] More recently, evidence on a range of risk reduction interventions on HCV seroconversion including behavioural interventions, NSP and OST were reviewed.[12] This study measured the effect of NSP use, defined inconsistently as any attendance of NSP or attendance at one point in time and showed increased risk of seroconversion. Limitations of this review included substantial heterogeneity across studies, a lack of clarity on the measure of NSP use and a focus on evidence from North America limiting the generalisability of findings to other settings including the UK. Our review on the effect of OST use on HIV transmission detected many more studies than earlier Cochrane reviews.[9] We also expect that not all evidence on the effect of NSP on HCV transmission has been identified so extending previous reviews would strengthen the evidence base as well as providing a more refined measure of coverage of NSP that accounts for frequency and the degree to which the NSP meets individuals requirement for needles/syringes.

A recent analysis of pooled data presented a clearer definition of NSP use, defining coverage in terms of the proportion of injections with a sterile syringe. This analysis suggested that high coverage of NSP (‘100% NSP’ - i.e. obtaining ≥1 sterile syringes per injection) or OST can each reduce HCV infection risk by 50%; and in combination by 80%. [13] However, due to a small number of incident HCV cases (n=40), the efficacy estimate for 100% NSP was weak (95% confidence interval 0.22–1.12), and there was insufficient power to evaluate whether a dose response relationship exists. This project will provide a more robust understanding of the likely impact of existing coverage levels of NSP and changes in the extent of provision.

There have been no attempts to estimate the cost-effectiveness of NSP provision in England, although NSP and OST are the current primary interventions for reducing HIV/HCV transmission among PWID in the UK. [5] In addition, although a recent NICE evaluation considered the cost effectiveness of NSPs, they were unable to estimate the incremental cost-effectiveness of increasing coverage because of ‘a paucity of evidence underpinning effectiveness’. [14] Internationally, among the economic evaluations of NSPs, none have been undertaken in Western Europe, few have considered the costs saved due to care and treatment averted, and all existing studies have relied on weak measures of NSP effectiveness. For example, either using changes in self-reported syringe sharing, or using ecological data relating NSP exposure to HCV prevalence or incidence in the population, which are unreliable and subject to substantial bias. [15] There is an urgent need to fill this

evidence gap by producing the first western European evidence for the cost-effectiveness of NSP and economic evaluation to use empirical data on NSP effectiveness in reducing HCV transmission at the individual level.

1.2. Risks and benefits

This study will provide the first robust evaluation on the impact of needle/syringe provision through NSPs on incidence of Hepatitis C among PWID and the costs associated with the service. These data will substantially improve the existing evidence base to inform harm reduction policies that will be beneficial to PWID and service providers. However there may still be uncertainty in the findings that will need to be considered. We will attempt to reduce uncertainty by employing multiple approaches to assess the impact of coverage on HCV incidence including logistic regression models as well as deterministic models and by conducting sensitivity analyses to validate the model. The study draws on data collected by public health surveillance systems, which collect only limited self-reported behavioural data. Asides from the limitations associated with self-reported behaviours, we are also limited in our measurement of the effect of NSPs to provision of clean needles/syringes only, which does not accurately reflect the multiple services that NSPs provide. If a positive effect of provision of needle/syringes on HCV incidence is found then we need to ensure that this finding is not interpreted to mean that other aspects of NSP services are underplayed. Working with the Hepatitis C Trust, Addaction and the National Needle Exchange Forum will ensure that findings are directly relevant to service providers and users.

1.3. Rationale for current study

Evidence of the effect of NSP use on HIV and HCV incidence is inconsistent. [16, 17] Studies have lacked sufficient evidence on the frequency of use of the intervention, the quantity of needles/syringes distributed, [18] or insufficient sample sizes to accurately measure the effect. [5] Economic evaluations of NSPs have not focussed on Western European data and existing studies have relied on weak measures of NSP effectiveness. Further evidence is essential in order to accurately estimate what level and combination of intervention is needed to substantially reduce HCV infection in PWID and the costs associated with increasing coverage to the optimal level.

2. Research Objectives

The aim of this proposal is to assess the impact and costs of different coverage levels of needle/syringe provision on the incidence of hepatitis C among people who inject drugs (PWID).

There are 6 linked objectives:

Objective 1) Using pooled datasets and a deterministic model measure the impact of different needle syringe programme coverage levels in the presence and absence of OST, on the incidence of hepatitis C among PWID in the UK.

Objective 2) Estimate the contribution of risk factors (e.g. homelessness, and crack use) to HCV incidence and the overall transmission of HCV among PWID.

Objective 3) Conduct a systematic review of international evidence on the impact of needle syringe programmes with and without opiate substitution therapy (OST) on incidence of hepatitis C among PWID.

Objective 4) Estimate the costs associated with existing NSP provision in three UK settings.

Objective 5) Estimate the impact and cost-effectiveness of existing provision of NSP, compared to no provision, on HCV and HIV transmission and disease burden among PWID in three UK settings

Objective 6) Determine possible strategies for increasing the coverage of NSP provision in three UK settings, and likely impact and cost-effectiveness of these strategies.

3. Research Design

The aims and objectives listed above will be achieved through the implementation of three linked data collection activities and analyses: 1) Analysis of Pooled data sets; 2) Systematic Review; and 3) Modelling Impact and Economic analysis.

4.1. Pooled analysis (Objectives 1 and 2)

This study utilises existing data sources on NSP use to measure the effect of different NSP coverage levels on HCV incidence among PWID. Data will be collated from the following sources:

1. Health Protection Agency's unlinked anonymous monitoring (UAM) survey of PWID (England, Wales and Northern Ireland, 2011 & 2012) [19, 20];
2. Health Protection Scotland's Needle Exchange Surveillance Initiative (NESI, 2008-2012) [21];
3. Five studies of community-recruited PWID in Birmingham, Bristol, Leeds and Wales (2004-2009) [22-27].
4. Australian NSP Survey (ANSPS, 2012) [28]

Methods of data collection

*Behavioural data***:** The UAM, ANSP and NESI collect behavioural data through a short self-completed questionnaire covering demographics, injecting and sexual risk, history of HIV and HCV testing, and current and previous HCV and drug treatment, designed to be quick and easy to complete. More detailed behavioural data are collected as part of community surveys. These are either self completed by hand or using computer assisted survey instruments.

Quality of data: Systems to ensure data from completed questionnaires are recorded accurately include double entry of questionnaire responses (UAM, ANSP, community surveys) and verification by a third person (UAM) or with software (ANSP). Data are not double entered in NESI but responses are checked with the interviewer prior to data entry.

Response rate: Completion of questions estimate coverage of NSPs is high among current injectors: 91% in the UA and 99% in NESI. Response rate was lower in ANSP at 65%, but in 2012 these items were simplified and the response rate is expected to be higher. Completion of other items such as frequency of injection or age is high in all surveys at >95%.

Measurement of HCV: All surveys use dried blood spots to measure anti-HCV.

Exposure

Measuring coverage by NSPs of PWID is problematic, standard definitions of coverage to include the proportion of the target population in need of the intervention that receives that intervention is difficult to estimate, since there is no explicit sampling frame of people who inject drugs, so estimating the extent of need is problematic. [29] A measure of an individual's NSP coverage will be defined as the percentage of his/her injections for which a new needle had been obtained from a NSP (calculated as the average number of new needles obtained from NSP divided by the average number of injections in the last 4 weeks). Recent evidence suggests that up to 25% of HCV infection could be averted by eliminating shared use of syringes.[1] Our definition of coverage therefore addresses the primary risk factors associated with HCV incidence and is a standardised measure used internationally which will facilitate comparison of findings to other studies. [30-32]

Measurement of outcomes

The outcome of interest is new HCV cases defined as PWID without HCV antibody (anti-HCV) but with HCV RNA in Polymerase Chain Reaction testing. [23] All data sources contain

data on new HCV cases, except the UAM, from which a sample of ~1,800 antibody negative dried-blood spots collected during 2011-2012 will be tested for this study.

The UAM collects capillary blood Guthrie cards (Whatman 903™ paper) from participants by fingerstick using a self-retracting single use lancet. Anti-HCV testing was performed using a previously published method whose accuracy is close to that achieved on venous blood specimens. [33] The residual DBS have been stored refrigerated with desiccant since anti-HCV antibody testing, which has been shown to stabilise both anti-HCV and nucleic acids in DBS. Nucleic acid will be extracted from an area of approximately 28 mm^2 punched from each DBS, using an automated platform (Qiagen MDx). Samples will be tested for HCV RNA employing nested PCR amplification of the NS5B region, which will provide a product suitable for differentiating different lineages of HCV. [34]

Proposed sample size

A sample of people who had injected in the last 4 weeks will be included from existing studies. Participants are either recruited via public health monitoring surveys in NSPs and other services (n=12,000) or one-off community surveys (n=1,667). Approximately 13,500 will be included in the analysis with ~6,400 being anti-HCV negative and ~160 recent infections. About half will have >=100% NSP coverage. The sample has >80% power to detect a decrease in risk of 20% for each increase in unit coverage (from <50% to over 150%) and a halving of risk between PWID exposed to <50% coverage compared to >150%.[13]

Statistical analysis

We will use logistic regression to model the odds of recent infection by NSP exposure.[35] Adjusted analyses will include key confounders of HCV risk (e.g. injecting duration and homelessness) and assess joint effects of OST. NSP coverage will be aggregated as categories (e.g. <50%, 50-100%), as well as a continuous variable. We will explore whether there is a dose response relationship (or linear decrease) in the odds of infection with increasing NSP coverage. We will also examine the impact of OST. A secondary analysis will focus on examining the effect of coverage on bacterial infections. Existing linkage between successive rounds of NESI and the Welsh cohort will also be used to estimate the proportion of PWID who change intervention or risk state between successive surveys Adjusted odds ratios will assess predictors for PWIDs changing state.

4.2. Systematic Review (Objective 3)

We will conduct a systematic review to measure the effect of use of NSPs with and without the provision of OST on the prevalence and incidence of HCV among PWID. Outcomes of interest include HCV incidence and prevalence. We will conduct the systematic review following Cochrane guidelines (http://cdag.cochrane.org/) and provisionally have registered the review. The systematic review will complete the gap in existing review evidence on the impact of NSPs and OST on transmission of HCV. Estimates from the pooled analysis will be used in a meta-analysis within the systematic review; this will enable us to assess the generalisability of the findings to an international context.

Papers will be identified in four ways. Firstly we will draw on findings from a Review of Reviews. [5] Second, we will conduct a primary search of the literature based on key search terms identified by the review of reviews and recent reviews of the effect of OST and NSP on the risk of HIV among PWID. We will conduct a systematic search of primary literature of the following databases: Medline, Cinahl, Psychinfo and the Cochrane Library. To identify articles we will combine three broad search themes with the Boolean operator “AND” and “OR”.

1. Theme 1 will combine the MeSH terms "Needle-Exchange Programs", “Community pharmacy service” with the free word terms “harm reduction” syringe*”, “syringe*”, “exchang*”, “secondary distribut*”, “indirect exchang*”, “ outreach”, “drop boxes”, “vending machines” combined with “OR”.
2. Theme 2 will combine the MeSH terms “Opiate Substitution Treatment, “Bupernorphine,” “Methadone with the free word terms “methadone maintenance” opiate substitut* therapy” combined with “OR”.
3. Theme 3 will combine the MESH terms "Hepatitis”, “Hepatitis C” with the free word terms “hepatitis C virus”, “hepatitis C antibody”, “hepatitis C”, “HCV” with “OR”

Third, we will identify longitudinal studies of PWID that report HIV or HCV as an outcome in order to determine whether information was provided on NSP in a table but not as a main result and/or ask the study authors whether information on NSP exposure was collected but not reported. In our review of OST and HIV this successfully identified a further eleven studies compared to an earlier Cochrane review, and provided a quantitative assessment on an additional 924 HIV seroconversions in over 25,660 additional person years of follow up permitting a meta-analysis.

Fourth, publications of key international agencies will also be searched including the European Monitoring Centre on Drugs and Drug Addiction, European Centre for Disease Control, the National Institute on Drug Abuse, the US Institute of Medicine, the United National Office on Drugs and Crime Prevention and the World Health Organisation. Researchers working in those organisations also will be contacted to identify public health surveillance data and contacts that may be published in the grey literature. We will also contact known experts in the field, including selected authors of key articles identified by the review, to identify any other relevant literature, including unpublished and policy sources. An example of the people to be contacted include members of the UN Reference Group on HIV/AIDS and international experts such as Louisa Degenhardt, Don Des Jarlais, Holly Hagan, Robert Heimer, Thomas Kerr, Alex Kral, Evan Wood.

Quality Assessment

The review will be conducted in accordance with PRISMA guidelines. [36] For all evidence we will assess the quality of included studies, including internal validity checks such as independent assessment by two reviewers of 10% of included papers. Detailed information extracted on the methods will be used to assess the quality of studies for inclusion in the review following methodologies such as the Newcastle-Ottawa. [37]

Data extraction

We will extract data on: a) population definition; b) intervention; c) methods (study design, sampling strategy, recruitment method, sample size, data collection method, generation of HCV antibody test); d) definitions; e) study limitations; f) unadjusted or adjusted effect size (Odds ratio, Rate ratio, hazard ratio).

Statistical Analysis

Effect estimates will be transformed into the natural log scale and used in a meta analysis using a random effects model. [38] Pooled effect estimates will be transformed back to original scale using exponentiation. Heterogeneity will be assessed using I^2 statistic to measure the total variation between study effect sizes that is attributable to heterogeneity. Bias in included studies will be assessed using a funnel plot. We will conduct a sensitivity analysis to examine the effect of study on various factors. These will be precisely defined depending on the extent and nature of included studies but are likely to include: quality of study, type of outcome measurement scale and using adjusted over unadjusted estimates. Analysis will also be stratified by time period for recruitment and measurement of NSP

exposure or geographical location. We will incorporate the pooled analysis results into the meta-analysis to determine the generalisability of our findings internationally.

4.3. Modelling Impact and Economic analysis (Objective 1, 2, 4, 5 and 6)

Modelling impact analysis: impact of provision (Objective 1, 2 and 5)

We will adapt an existing dynamic deterministic model of HCV and HIV transmission and OST/NSP intervention coverage among PWID [14, 39, 40] to consider additional levels of NSP coverage and HCV or HIV transmission risk). PWID will be considered in any combination of intervention (use of NSP with/without OST) and risk state (being in any state shown to be associated with an increased or decreased risk of HCV transmission in the pooled analysis) over time. [39] PWID will become infected with HIV and HCV at a rate dependent on their level of intervention and risk state, the degree of mixing between PWID of different risk levels and the HIV and HCV prevalence of PWID in reach risk and intervention state. [24] We will assume that HCV is transmitted through injecting risks but sexual transmission of HIV will also be considered. The infectivity of a person with HIV infection will be elevated if they are in the initial or pre-AIDS high viraemia stages of HIV infection and HCV infectivity may be elevated if they are co-infected with HIV. [40, 41] The proportion of HCV that will spontaneously resolve infection or that achieve a sustained viral response following treatment will be reduced among PWID co-infected with HIV [42] and their progression to cirrhosis will be elevated. ART will also be assumed to reduce HIV progression and HIV infectivity. [43]

The model will be parameterised to 3 UK settings (Bristol, Dundee and Cardiff) using data from the UAM survey [19, 20], NESI [21] and other community-based surveys.[22-27] Intervention efficacy estimates will be estimated from the pooled analysis, based on the literature and remodelled using the pooled analysis. [6, 8, 9, 13] The 3 settings provide a range of HCV prevalence and there is comprehensive behavioural data available in order to parameterise the models. In Bristol prevalence of HCV is between 60-65%, estimated through three rounds of community-based surveys in 2004, 2006 and 2009, [22-24] Prevalence of HCV is between 20-35% in Cardiff and was included (n=185) in the Welsh cohort study. [25] In Dundee prevalence of HCV is between 30 and 40%. Enhanced surveillance will be will be conducted in the 2013 and 2014 as a site of a HCV treatment trial (n=250). All three sites participate in the UAM survey (Bristol and Cardiff (n=150 and 80 respectively) and Dundee in the NESI surveys in 2007, 2008/09, 2010 (n=150). [20]

Data on how PWID transition between different intervention and risk states will be derived from the Welsh and London cohort studies and analysis of linked data on individuals across successive round of NESI. [21, 44] HCV treatment coverage and sustained viral response rates will come from recent data collected among PWID as part of a NIHR project grant held by a co-applicant, Matthew Hickman. Data on HIV and HCV transmission and progression parameters, and HCV or HIV treatment effects will come from the scientific literature, all of which has been reviewed recently for previous modelling analyses. [40, 45-47]

All parameters will have uncertainty ranges associated with them. Using Bayesian fitting methods[40], incorporating likelihood measures to assess goodness of fit, [48] the model will be calibrated to HCV prevalence trends for each setting while accounting for any changes in the prevalence of behaviours linked to HCV transmission risk (e.g. homelessness, crack use) and levels of intervention coverage (OST and NSP provision). The models will also be fit to data on the prevalence of HIV in each site [19, 22]. However, as the level of HIV transmission is thought to be low in all 3 settings, the models will only be calibrated such that they produce a prevalence of HIV below a certain minimum level.

Multiple model fits will be used to estimate the impact of historical and current NSP coverage levels for reducing HCV and HIV prevalence and disease burden in that setting. This will be

done by creating a counterfactual for each model fit where the coverage of NSP provision remains at negligible levels, and comparing the disease outcomes and projected HCV/HIV prevalence trends with the corresponding model fit. The future impact of increasing/decreasing NSP coverage levels will also be estimated by comparing a scenario where the coverage of NSP remains stable with a range of scenarios where the coverage of NSP increases or decreases from 2013 over 5, 10 and 20 years (used for objective 6).

Modelling impact analysis: contribution of other risk factors (Objective 2)

The model fits for each setting will also be used estimate the contribution of different risk factors that may increase individual HCV transmission risk in the pooled analysis (e.g. homelessness and crack use have been shown to be associated with elevated HCV incidence and prevalence risk in the UK. [13, 22] Comparisons between model projections that do or do not include the elevated transmission risk associated with these risk factors will be used to assess their importance. This will be done either instantaneously at certain time points to estimate the short term population attributable fraction of these risk factors, or over longer timeframes to evaluate its overall contribution to the disease burden amongst injectors in each setting.

Economic analysis

The objectives of the economic analysis are three-fold. Firstly we estimate the cost-effectiveness of current NSP provision, compared to no provision, in 3 UK settings (objective 4) and secondly, the potential cost-effectiveness of increasing NSP coverage in these sites, versus stable coverage (objective 5) and the potential cost–effectiveness of different possible strategies for increasing NSP coverage in these sites, versus stable coverage (objective 6).

For all analyses, health benefits (quality-adjusted life years, QALYs) and costs (health care provider perspective) will be attached to each HCV and HIV disease stage as undertaken in previous analyses [46], and we will use recently published utility weights for injectors. [49] Following NICE guidelines, costs and utilities will be discounted at 3.5%, with a time horizon of 100 years for estimating future benefits/costs. [50] Economic model results will be presented as incremental cost-effectiveness ratios (ICER). Probabilistic uncertainty analyses will be used to estimate the uncertainty around the ICER, and the probability that the intervention is cost-effective for different willingness-to-pay thresholds (£20,000 or £30,000 per QALY as used by NICE). A range of sensitivity analyses will be done to consider the effect of important parameters such as the time horizon, discount rates, duration of injecting, baseline HCV and HIV prevalence and level of risk heterogeneity.

Estimate the costs of existing NSP provision in 3 UK settings (Objective 4)

Current NSP intervention costs and output data will be collected from the 3 UK settings over one year using an ingredients methodology.[51, 52] This will incorporate the costs for different modalities of NSP provision (pharmacy, specialised and mobile site). For pharmacies, only a sub sample will be costed in detail due to there being multiple pharmacy NSPs in each setting (>20 in each). The costs of other pharmacies will be estimated using their output data and unit cost data from the pharmacies where detailed costings were undertaken. The incremental cost of undertaking NSP services in each setting will be estimated from the provider perspective for all activities linked to the running of the NSP. Building rental, equipment and vehicle costs will be included if they are specific to the NSP, but only a proportion will be attributed to the NSP if they are used for other activities. Their values will be taken from expenditure records and annualized over their expected useful life using the discount rate of 3.5%. Training costs will considered and annualized using the same methodology. The costs for producing educational materials will be included. Staff

costs will be taken from expenditure records, but only the staff time attributable to running the NSP will be included. This will be estimated through interviews and observing activities. Any volunteer costs will be calculated according to the number of days worked and an appropriate measure of their opportunity cost. The total costs of needles and syringes distributed will be estimated as the number distributed multiplied by the current price including transport costs. Overhead costs will also be estimated and uncertainty will be attached to all cost estimates when appropriate. The average cost of each service modality in each setting will be calculated as cost per contact (annual number of contacts made) and cost per syringe distributed.

Estimate the cost-effectiveness of existing NSP provision, compared to no provision, in 3 UK settings (Objective 5**)**

Annual NSP cost estimates will be extrapolated for future years, and combined with model estimates of the impact attributable to current levels of syringe provision in each setting over 1, 3, 5 and 10 years. The impact of current NSP provision will be estimated for each setting by comparing the projected trends in HIV and HCV transmission if NSP coverage remained stable to those that could occur if all PWID had negligible syringe coverage. More details of the methods for estimating impact are included in the previous section on the impact analysis.

Estimate the potential cost-effectiveness of different possible strategies for increasing NSP coverage in three UK settings, versus coverage remaining stable (Objective 6)

NSP modality, costs and syringe distribution data from the sites (Bristol, Cardiff and Dundee) will be compared to consider factors that may increase or decrease syringe distribution output for a specific type of NSP provision or across the different settings. This analysis will be undertaken with and supplemented by consulting and collaborating with NSP service providers and service users in each setting and other individuals and organisations with expertise in this area (NNEF, Addaction, Scottish Drugs Forum, WNEF), and through reviewing the literature on interventions or NSP characteristics that can improve syringe distribution or coverage (review currently being undertaken by NICE). Possible factors that may increase NSP distribution include longer opening hours, changing location and/or increasing NSP density, mobile site distribution, and use of specialist drug staff. [4] An important part of this process will be a collaborators meeting where we will firstly present the results of our pooled analysis and cost-effectiveness estimates for existing levels of NSP provision, and secondly we will discuss possible factors that could or have increased coverage. This will help develop possible modelling scenarios for improving intervention coverage.

The costs (including implementation and increased activity) of different changes to NSP provision (agreed in consultation with providers and service users) in our sites will be estimated and the potential impact of the increase in syringe coverage modelled. The projected extra costs will be based on our detailed cost data collected from the three sites and the estimated additional resources (staff time, increase in pharmacies, vending machines) needed to improve that specific aspect of NSP provision. The increase in syringes distributed or proportion of IDUs with high syringe coverage will be estimated from observations on how an implemented change in NSP provision increased coverage in a specific setting (our model sites or other sites) or how differences in provision between settings may have affected the coverage achieved in a setting. The increase in resource needs and coverage will be estimated through consultation with our local and national providers and through reviewing any relevant literature.[4, 53] For Wales and Scotland, data from their NEO database (contains computerised anonymised data on all PWID that attend NSP services, how frequently and when/where they attend different providers, number of syringes exchanged, and data on self–reported injecting frequency) may help provide data

on how any specific change or difference in NSP provision across Wales and Scotland may have increased the number of PWID that attend a service or the number that have high syringe coverage. Otherwise, data on how the volume of syringe distribution and number of contacts could increase will be used to simulate a range of scenarios on how the proportion of PWID with different levels of syringe coverage could change for a specific change in NSP provision. These scenarios will be modelled to produce a range for the incremental impact of improving a specific aspect of the NSP service. Outputs from this analysis will be used to project the possible incremental cost-effectiveness ratio for different strategies for increasing NSP provision in our 3 chosen settings, compared to coverage remaining stable.

4. Intervention being evaluated

The intervention to be evaluated is NSPs providing sterile injecting equipment to PWID in community settings. The current primary interventions for reducing HIV/HCV transmission among PWID are opiate substitution therapy (OST) and NSP. [5]In 2005, there were an estimated 1,700 NSPs in England, 70% of which were provided by community pharmacies, with the rest offered by specialist community-based services, outreach/mobile services and in custody suites. [54] NSPs in England are funded through Drug Action Teams (DATs) and Local Strategic Partnerships – multi-agency bodies involving local government, police, and health services.

5. Study population

The study population are people who currently inject drugs, defined as injection in the last 4 weeks and who have participated in either the UAM, NESI, ANSP or one of the five community surveys. All eligible NSP attendees are asked to take part in the three surveillance surveys. NSPs attendees are eligible to take part if they have injected drugs on a least one occasion and can only participate once during the annual survey period. For the UAM and NESI, data collection takes place throughout the year; in ANSP it takes place annually over a one-two week period in October. Participants are recruited from the majority of services providing injecting equipment in each site. For example, NESI recruits from 103/208 services and 53/85 NSPs in Australia. Eligibility criteria for participation in the community surveys were restricted to those who had injected in the last 4 weeks. All analyses will focus people who have injected in the last 4 weeks only.

6. Socioeconomic position and inequalities

Injecting drug use is a major global health concern, with between 11 and 21 million people injecting drugs worldwide. Overall, there are an estimated 4.8 million people who inject drugs (PWID) in the European region.[55] Engaging in behaviours that are socially stigmatised and illegal PWID are a highly vulnerable and marginalised population. PWID have high rates of unemployment, homelessness and have frequently been in prison factors that further entrench vulnerability and marginalisation increasing inequalities in health. [2] Blood borne viruses, including Hepatitis C, contribute significantly to the excess morbidity and mortality experienced by PWID.[56-58] Hepatitis C virus is a major cause of liver disease in the UK, with over 200,000 people chronically infected and injecting drug use accounting for 90% of infections.[59] Prevention of HCV transmision among PWID is therefore critical to slowing the growing burden of liver disease.[60, 61]

NSPs are essentially the first stage intervention to reduce inequalitaties in health for PWID, they provide a first point of contact for PWID, providing clean needles/syringes to prevent immediate risk infection with blood borne viruses reducing bacterial infections as well as engaging with users to make onwards referrals to other needed medical, drug treatment or social support services. This study will provide essential evidence for the first time to assess the effect of NSPs on reducing HCV incidence and as a consequence further the evidence for the most effective and cost-effective way to reduce inequalities in health.

The large sample size included in the study from England, Wales, Scotland will ensure a diverse section of PWID in treatment are included from a range of services (including needle/syringe exchanges and specialist drug treatment programmes). Approximately a third of the sample are women who inject drugs and approximately 10% have experience of sex work. The use of the five community surveys of PWID recruited from non treatment settings ensures that this population of drug users are not missed, an important contingent since the evidence suggests that PWID not in treatment engage in higher risk injecting risk behaviours than those in treatment.

7. Ethics:

Participants are provided information about the survey and give verbal consent. Participation is anonymous and voluntary. Financial reimbursement is not provided, although some services provide non-monetary incentives to participants such as on-site food and drinks, food or movie vouchers, or injecting-related items that are not freely available from the NSP. All surveys have appropriate ethical approval from appropriate sites including: London Multi-Centre Research Ethics Committee (MREC/98/2/51), the NHS West of Scotland Research Ethics Service (April 2008) and the University of New South Wales Human Research Ethics Committee (HREC) and relevant jurisdictional and site-specific ethics committees for individual sites and the community surveys. These ethical approvals allow for the storage of samples and subsequent testing.

8. Research Governance

The London School of Hygiene and Tropical Medicine as the employing institution of the lead applicant, through Professor Richard Smith, Dean of the Faculty of Public Health and Policy will take the role of sponsor. All co-investigators and collaborators will meet twice during the course of the project to discuss the programme of work. Our team is multi-disciplinary comprising academics working in the disciplines of economics, epidemiology, mathematics and statistics as well as public health surveillance experts, virologists, people working in provision of NSPs and advocates for people living with HCV. They will meet twice and be in constant communication to advise on the project. We therefore judged it unnecessary to convene a separate study steering committee particularly considering the short time-frame of the project.

9. Project timetable and milestones

The project will be conducted over 24 months: 6 months for data pooling and statistical modelling, 4 months systematic review and write-up, 10 months for impact and cost-effectiveness modelling and write-up. 10 months for cost data collection, cost modelling and write-up. There will be 2 project meetings with the co-investigators, and a meeting at each of the 3 sites with service providers and collaborators. Three peer-reviewed publications will be produced from the study and findings will be presented at the International Conference on Drug Related Harm in April 2015. A detailed timetable of activities and outputs is presented below.

Activity	Year 1											
	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEPT	OCT
Contracts agreed												
HPA testing of 2012 UA survey data												
Meeting of co-investigators and collaborators												
Local data cleaning												
Collation of cost data for 3 sites												
Pooling data: NESI, UAM, ANSPS, community surveys												
Meeting of co-investigators and collaborators												
Pooled analysis												
Systematic Review												
	Year 2											
Systematic Review												
Output 1: Pooled analysis												
Comparison with systematic review												
Output 2: Systematic review												
Impact modelling of coverage												
Cost effectiveness analysis												
Discussion on scale up with service providers/collaborators												
Modelling scale up scenarios												
Output 4: Modelling and economic evaluation												
Output 5: Conference presentation												
Output 6: Policy brief												

10. Expertise

Dr Lucy Platt (LP) has extensive experience in managing large surveys of PWID with linked biological and behavioural data and conducting systematic reviews. In collaboration with Peter Vickerman (PV) she will oversee the day to day management of the project and overall study design. LP will lead the systematic review, data cleaning and risk factor analysis of pooled data.

Dr Peter Vickerman has considerable expertise in modelling the transmission of blood borne infections among PWID and in undertaking cost-effectiveness analyses of a wide range of HIV, STI and HCV intervention strategies. He will be responsible for the mathematical modelling, assessing the impact of current NSP provision on HCV infection and the analysis of impact of scaling up the intervention. PV and LP will supervise the work of a research fellow undertaking the mathematical modelling.

Dr Lorna Guinness is experienced in costing analyses of harm reduction interventions among PWID determining the cost drivers between interventions in different settings. She will be responsible for assessing the costs of provision of NSP in 3 settings and analysis of costs of different coverage levels of NSP provision. LG, in collaboration with PV and LP, will supervise the work of a research assistant undertaking the cost and cost-effectiveness analysis.

Dr Vivian Hope coordinates the design, implementation and analysis of data from the unlinked anonymous monitoring (UAM) among PWID in England and Wales at the Health Protection Agency (HPA). He will be responsible for data extraction of the relevant data from the UAM to be used in the analysis. Dr Fortune Ncube is an epidemiologist at the Health Protection Agency responsible for the surveillance of infections among PWID across England. Both FN and VH will advise on the design of the project and ensure that recommendations from the study will be incorporated into future surveillance of HCV among PWID. Professor John Parry will be responsible for the PCR testing of 2000 antibody negative samples from the UAM survey for RNA to detect new cases of HCV.

Co-investigators responsible for routine data collection will contribute their expertise to the field in terms of providing data, assisting in the design, analysis and interpretation of findings as well as write up. This includes key experts in the field: Prof. Matt Hickman responsible for the community surveys of PWID in England; Dr Sharon Hutchinson and Prof Avril Taylor responsible for Needle Exchange Survey Initiative in Scotland; Professor Lisa Maher coordinator of the Australian Needle Syringe Programme Survey; Noel Craine coordinator for public health monitoring of blood borne viruses among PWID in Wales and Josie Smith Research Scientist at Public Health, Wales.

11. Partner Collaboration

We will collaborate with Addaction, a charity that runs a national network of community-based drug and alcohol services across the UK, including approximately 60 Needle Syringe Programmes across England. We will also collaborate with the National Needle Exchange Forum (NNEF) and the UK Harm Reduction Alliance (UKHRA), collectively they comprise a group of needle exchange workers from England that exist to actively promote and support the provision of high quality, comprehensive needle/syringe programmes as a key part of the United Kingdom drugs strategy. They engage in advocacy work to raise awareness and promote understand of needle exchange as well as identify and promote good practice in the development and delivery of NSPs.

Addaction will both provide advice, support and assistance with the collection of cost data on needle/syringe programmes that are collected routinely by the services they fund. NNEF and UKRA will facilitate communication with their services and members in order to collect data on costs. Their collaboration is essential in order to provide the perspective of service providers into the design of the study, the analysis and interpretation of the findings to ensure that findings have direct policy relevance. The services will also provide a conduit to involve people who inject drugs in the study by informing them of the study and feeding back findings through meetings or publicity on their web sites. Key findings from the analysis will be included in policy reports published on the web-sites to ensure that findings are disseminated to PWID and service providers.

We will also collaborate with the Hepatitis C Trust, a charity that provides support to people living with HCV, information to populations vulnerable to HCV infection on the importance of testing as well as advice about treatment and advocacy work to reduce the stigma associated with HCV. The Trust will provide a route for people living with HCV to contribute to the design of the study and will contribute to the meetings of co-investigators. They will use their peer education programme and website in order to disseminate findings of the research to people living with hepatitis C. Their role will also be to ensure that other prevention initiatives that NSPs provide, such as the provision of clean injecting paraphernalia, health promotion information on injecting practices and the need for testing for hepatitis C are also considered in the research to ensure the provision of needles/syringes within a full range of interventions. Each organisation's support for the project has been confirmed as indicated in the attached letters of support.

.

References

1. Pouget, E.R., H. Hagan, and D.C. Des Jarlais, *Meta-analysis of hepatitis C seroconversion in relation to shared syringes and drug preparation equipment.* Addiction, 2012. **107**(6): p. 1057-65.
2. Strathdee, S.A., et al., *HIV and risk environment for injecting drug users: the past, present, and future.* Lancet, 2010. **376**(9737): p. 268-84.
3. Gibson, D.R., N.M. Flynn, and J.J. McCarthy, *Effectiveness of methadone treatment in reducing HIV risk behavior and HIV seroconversion among injecting drug users.* Aids, 1999. **13**(14): p. 1807-18.
4. Jones, L., et al., *A review of the effectiveness and cost-effectiveness of needle and syringe programmes for injecting drug users*, 2008, Centre for Public Health, Liverpool John Moores University: Liverpool.
5. Palmateer, N., et al., *Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews.* Addiction, 2010. **105**(5): p. 844-59.
6. Van Den Berg, C., et al., *Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users.* Addiction, 2007. **102**(9): p. 1454-62.
7. Gibson, D.R., N.M. Flynn, and D. Perales, *Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users.* AIDS, 2001. **15**(11): p. 1329-41.
8. Aspinall, E., et al., *Are needle and syringe programmes associated wth a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis.* In preparation, 2013.
9. MacArthur, G.J., et al., *Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis.* BMJ, 2012. **345**: p. e5945.
10. Tilson, H., et al., *Preventing HIV infection among injecting drug users in high-risk countries: an assessment of the evidence*2007, Washington: Institute of Medicine.
11. Wodak, A. and A. Cooney, *Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users*, in *Evidence for Action Technical Papers*2004, World Health Organisation Geneva.
12. Hagan, H., E.R. Pouget, and D.C. Des Jarlais, *A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs.* J Infect Dis, 2011. **204**(1): p. 74-83.
13. Turner, K.M., et al., *The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence.* Addiction, 2011. **106**(11): p. 1978-88.
14. Vickerman, P., A. Miners, and J. Williams, *Assessing the cost-effectiveness of interventions linked to needle and syringe programmes for injecting drug users: An economic modelling report*, in *NICE public Health Guidance 18 (http://www.nice.org.uk/nicemedia/live/12130/43370/43370.pdf)*, National Institute for Health and Clinical Excellence, Editor 2008: London.
15. Guinness, L., et al., *Systematic review of the cost-effectiveness of interventions to reduce the health harms of injecting drug use.* In preparation 2012.
16. Committee on the Prevention of HIV infection among Injecting Drug Users in High-Risk Countries, *Preventing HIV Infection Among Injecting Drug Users in High-Risk Countries: An Assessment of the Evidence*, 2007, Institute of Medicine Washington, DC.
17. Mathers, B.M., et al., *HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage.* Lancet, 2010. **375**(9719): p. 1014-28.
18. Lurie, P., *Invited commentary: le mystere de Montreal.* Am J Epidemiol, 1997. **146**(12): p. 1003-6; discussion 1007-10.

19. Health Protection Agency, *Shooting up. Infections among injecting drug users in the United Kingdom 2009 (http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733837406)*, 2010: London.
20. Hope, V.D., et al., *HIV prevalence among injecting drug users in England and Wales 1990 to 2003: evidence for increased transmission in recent years.* AIDS, 2005. **19**(11): p. 1207-14.
21. Allen, E., et al., *Needle Exchange Surveillance Initiative (NESI): Prevalence of HCV and injecting risk behaviours among people who inject drugs attending injecting equipment provision services in Scotland, 2008/2009 & 2010.*, 2012, Health Protection Scotland Glasgow.
22. Hickman, M., et al., *Hepatitis C virus (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004.* J. Viral. Hepat, 2007. **14**(9): p. 645-52.
23. Hope, V.D., et al., *Measuring the incidence, prevalence and genetic relatedness of hepatitis C infections among a community recruited sample of injecting drug users, using dried blood spots.* J. Viral. Hepat, 2011. **18**(4): p. 262-70.
24. Mills, H.L., et al., *Respondent driven sampling and community structure in a population of injecting drug users, Bristol, UK.* Drug Alcohol Depend, 2012.
25. Craine, N., et al., *Incidence of hepatitis C in drug injectors: the role of homelessness, opiate substitution treatment, equipment sharing, and community size.* Epidemiol Infect, 2009. **137**(9): p. 1255-65.
26. Hutchinson, S.J., et al., *Prevalence of hepatitis C among injectors in Scotland 1989-2000: declining trends among young injectors halt in the late 1990s.* Epidemiol Infect, 2002. **128**(3): p. 473-7.
27. Roy, K.M., et al., *Hepatitis C virus infection among injecting drug users in Scotland: a review of prevalence and incidence data and the methods used to generate them.* Epidemiol Infect, 2007. **135**(3): p. 433-42.
28. Topp, L., et al., *Fifteen years of HIV surveillance among people who inject drugs: the Australian Needle and Syringe Program Survey 1995-2009.* AIDS, 2011. **25**(6): p. 835-42.
29. Donoghoe, M.C., et al., *Setting targets for universal access to HIV prevention, treatment and care for injecting drug users (IDUs): towards consensus and improved guidance.* Int J Drug Policy, 2008. **19 Suppl 1**: p. S5-14.
30. Heimer, R., et al., *Syringe use and reuse: effects of syringe exchange programs in four cities.* J Acquir Immune Defic Syndr Hum Retrovirol, 1998. **18 Suppl 1**: p. S37-44.
31. Aceijas, C., et al., *Access and coverage of needle and syringe programmes (NSP) in Central and Eastern Europe and Central Asia.* Addiction, 2007. **102**(8): p. 1244-50.
32. Bluthenthal, R.N., et al., *Higher syringe coverage is associated with lower odds of HIV risk and does not increase unsafe syringe disposal among syringe exchange program clients.* Drug Alcohol Depend, 2007. **89**(2-3): p. 214-22.
33. Judd, A., et al., *Evaluation of a modified commercial assay in detecting antibody to hepatitis C virus in oral fluids and dried blood spots.* J Med Virol, 2003. **71**(1): p. 49-55.
34. Mellor, J., et al., *Investigation of the pattern of hepatitis C virus sequence diversity in different geographical regions: implications for virus classification. The International HCV Collaborative Study Group.* J Gen Virol, 1995. **76 (Pt 10)**: p. 2493-507.
35. Turner, K., et al., *The impact of needle and syringe provision and opiate substitution therapy on the incidence of Hepatitis C virus in injecting drug users: pooling of UK evidence.* Addiction (web published ahead of print), 2011.
36. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* J Clin Epidemiol, 2009. **62**(10): p. e1-34.

37. Wells, G.A., et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.* . 2012 [cited 2012 January 30th]; Available from: http://www.ohri.ca/programs/ clinical_epidemiology/oxford.asp.
38. Der Simonian, R. and N. Laird, *Meta-analysis in Clinical Trials.* Controlled Clinical Trials, 1986. **7**: p. 177-188.
39. Vickerman, P., et al., *Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in HCV prevalence? Model projections for different epidemic settings.* Addiction, 2012.
40. Vickerman, P., L. Platt, and S. Hawkes, *Modelling the transmission of HIV and HCV amongst injecting drug users in Rawalpindi, a low HCV prevalence setting in Pakistan.* Sex. transm. Infect, 2009. **85**: p. ii23-ii30.
41. Hollingsworth, T.D., R.M. Anderson, and C. Fraser, *HIV-1 transmission, by stage of infection.* J Infect Dis, 2008. **198**(5): p. 687-93.
42. Thomas, D.L., et al., *The natural history of hepatitis C virus infection: host, viral, and environmental factors.* JAMA, 2000. **284**(4): p. 450-6.
43. Cohen, M.S., et al., *Prevention of HIV-1 infection with early antiretroviral therapy.* N Engl J Med, 2011. **365**(6): p. 493-505.
44. Judd, A., et al., *Incidence of hepatitis C virus and HIV among new injecting drug users in London: prospective cohort study.* BMJ, 2005. **330**(7481): p. 24-5.
45. Degenhardt, L., et al., *Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed.* Lancet, 2010. **376**(9737): p. 285-301.
46. Martin, N.K., et al., *Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations.* Hepatology, 2012. **55**(1): p. 49-57.
47. Vickerman, P., N.K. Martin, and M. Hickman, *Understanding the trends in HIV and hepatitis C prevalence amongst injecting drug users in different settings--implications for intervention impact.* Drug Alcohol Depend, 2012. **123**(1-3): p. 122-31.
48. Pickles, M., et al., *Interim modelling analysis to validate reported increases in condom use and assess HIV infections averted among female sex workers and clients in southern India following a targeted HIV prevention programme.* Sex Transm Infect, 2010. **86 Suppl 1**: p. i33-43.
49. McDonald, S.A., et al., *Decrease in health-related quality of life associated with awareness of hepatitis C virus infection among people who inject drugs in Scotland.* J Hepatol, 2012.
50. National Institute for Health and Clinical Excellence, *Needle and syringe programmes: providing people who inject drugs with injecting equipment*, in *NICE public health guidance 18*2009.
51. Drummond, M., G.L. Stoddart, and G.W. Torrance, *Methods for the Economic Evaluation of Health Care Programmes.* 1997, Oxford: Oxford Medical Publications.
52. United Nations Programme on HIV/AIDS (UNAIDS), *Costing Guidelines for HIV/AIDS Prevention Strategies* 2000, UNAIDS: Geneva.
53. Cooper, H.L., et al., *Spatial access to syringe exchange programs and pharmacies selling over-the-counter syringes as predictors of drug injectors' use of sterile syringes.* Am J Public Health, 2011. **101**(6): p. 1118-25.
54. National Institute for Health and Clinical Excellence, *Needle and syringe programmes: providing people who inject drugs and with injecting equipment*, in *NICE public health guidance 18*2009, National Institute for Health and Clinical Excellence.
55. Mathers, B.M., et al., *Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review.* Lancet, 2008. **372**(9651): p. 1733-1745.
56. Bargagli, A.M., et al., *Drug-related mortality and its impact on adult mortality in eight European countries.* Eur J Pub Health, 2006. **16**(2): p. 198-202.

57. Degenhardt, L., W. Hall, and M. Warner-Smith, *Using cohort studies to estimate mortality among injecting drug users that is not attributable to AIDS.* Sex Transm Infect, 2006. **82**(suppl 3): p. iii56-iii63.
58. Aceijas, C. and T. Rhodes, *Global estimates of prevalence of HCV infection among injecting drug users.* International Journal of Drug Policy, 2007. **18**(5): p. 352-8.
59. Health Protection Agency, *Hepatitis C in the UK*, 2011, Health Protection Agency: London: Colindale.
60. Shepard, C.W., L. Finelli, and M.J. Alter, *Global epidemiology of hepatitis C virus infection.* The Lancet Infectious Diseases, 2005. **5**(9): p. 558-567.
61. Advisory Council on Misuse of Drugs, *The Primary Prevention of Hepatitis C Among Infecting Drug Users*, in *Report No.: 97818472688392*009, Home Office: London.