Assessing the cost-effectiveness of interventions linked to needle and syringe programmes for injecting drug users:

An economic modelling report

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Executive Summary

Background

The aim of this report was to undertake cost-effectiveness analyses of interventions related to needle and syringe programmes (NSP) for injecting drug users (IDUs). The starting point was the associated 'effectiveness' report, completed by researchers at the Centre for Public Health, Liverpool John Moores University (LJMU). The effectiveness report sought to determine the optimal provision of needle distribution schemes among IDUs, and consisted of a systematic review of the effectiveness and cost-effectiveness literature. The following four questions were considered in the effectiveness report:

1. What level of coverage of needle and syringe programmes (NSPs) is the most effective and cost-effective?
2. What types of NSPs are effective and cost effective?
3. Which additional harm-reduction services offered by NSPs are effective and cost effective?
4. Are NSPs delivered in parallel with, or alongside, opiate substitution therapy (OST) effective and cost-effective?

Setting the objectives

These questions were also used as terms of reference for the cost-effectiveness analysis. However, because they were broad and non-specific about interventions, comparator programmes and specific IDU-groups, a

significant part of the analysis contained herein was dedicated to transforming them into a number of answerable 'decision problems'.

The decision problems were largely determined by considering: whether they would represent policies that would be useful additions to current UK NSP policies; the availability of suitable evidence on effectiveness (supplied by LJMU); the applicability of existing infectious disease models relating to IDUs. The availability of evidence on effectiveness was deemed important insofar as it was considered to be a prerequisite to any useful, rather than interesting, modelling. Access to appropriate IDU models was also considered to be a necessary consideration as it was recognised at the outset of the project that modelling the transmission of infections in IDUs is a complex issue and resources were not available to start the process from scratch.

The initial effectiveness report by LJMU identified 22 relevant studies. During the assessment process, a further 2 published studies and one unpublished study were identified meaning that a total of 25 studies were identified. The quality of the studies was generally judged to be poor, in terms of using them to derive estimates of effectiveness for cost-effectiveness modelling. For example, only 4 contained controlled studies and many assessed relationships between variables (such as syringe coverage and risky behaviour) but did not evaluate an intervention per se. Thus, the overall set of usable effectiveness studies was limited.

The decision was made to combine two models previously built by one of the authors (PV) as the basis for the economic analysis. Broadly speaking, one of these models previously assessed HIV transmission patterns in non-UK IDU populations, whereas the other model assessed HCV transmissions. The decision to use these models as a basis for the evaluation contained herein was important insofar as it meant that the effectiveness studies needed to report outcomes on which the models were based. For example, changes in the frequency of needle sharing could be accommodated within the model, but needle re-use could not as there is no obvious link between it and the transmission of viruses. It also meant that the decision problems could not include interventions to prevent bacterial infections or consider specific IDU-subgroups such those in prison.

Taking into account both the availability and the choice of infectious disease model, three decision problems were identified:

Decision problem 1: Is the intervention to increase participation in OST programmes amongst NSP clients, as broadly described in Strathdee et al, cost-effective compared with no specific encouragement to participate, in IDUs expressing an interest in receiving treatment for their injecting drug addiction?

Decision problem 2: What additional cost would be acceptable if it were possible to increase sterile syringe coverage for IDUs attending NSPs?

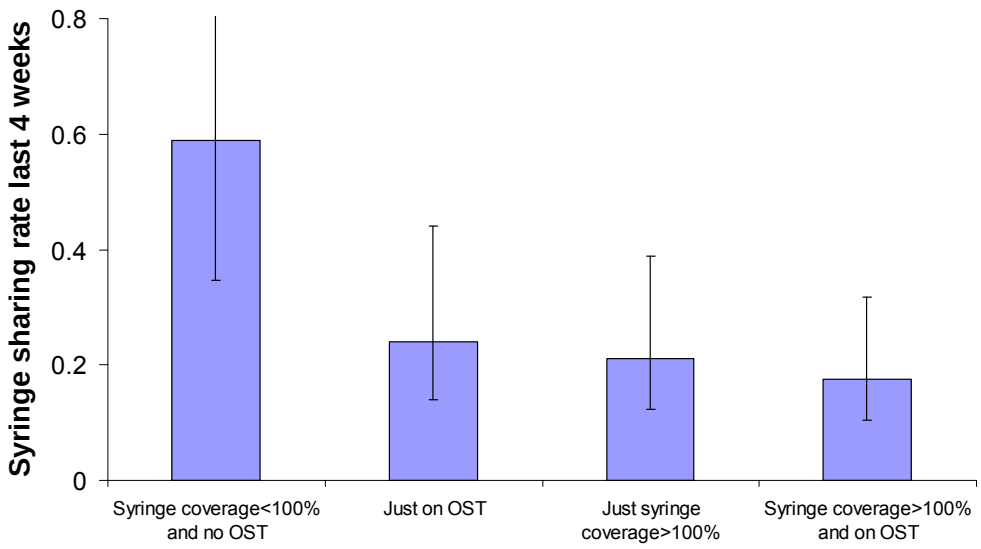
Decision problem 3: What additional cost would be acceptable if it were possible to increase the recruitment of HCV infected current IDUs onto HCV treatment through existing NSPs, as described in the unpublished study by Wilkinson et al.

Decision problem 1: The RCT by Strathdee et al. evaluated an intervention to increase participation rates to opiate substitution therapy (OST) in IDUs expressing an interest in OST. The intervention was termed a 'strengths-based management approach' and was compared with a standard referral letter / approach to OST. The primary outcome was the proportion of IDUs who attended an *initial* OST meeting within 7-days of referral (intervention 40% vs control 26%), no further follow-up data was collected.

Decision problem 2: The effectiveness review did not identify any studies that could be used to derive effectiveness estimates for a cost-effectiveness

evaluation of interventions to increase (or decrease) syringe coverage (defined as the ratio of number of syringes obtained for their own use compared to the frequency of injecting). However, the review and additional analyses of a number of cross sectional data sets from the UK did provide data on the likely positive correlation between syringe coverage, OST use and syringe sharing (Figure 1), and so generated sufficient information to undertake threshold analyses. So for example, it was possible to estimate the additional costs that would be acceptable if it were possible to increase the proportion of IDUs who were in 'high' rather than 'low' syringe coverage groups'.

Figure 1: Syringe sharing frequency for different levels of intervention participation in seven cities in the UK (unpublished results)



Decision problem 3: Threshold analyses was also undertaken for an intervention to increase the number of HCV positive current IDUs receiving antiviral therapy, as proportion of infected IDUs currently receiving HCV

treatment is very low. The effectiveness evidence was derived from a non-controlled unpublished UK based study by Wilkinson et al. Broadly speaking, the intervention recruited onto HCV treatment approximately 5% of infected IDUs attending the NSP each year, and of those IDUs who received treatment, compliance was greater than 80%. Moreover, of those in whom follow-up was possible at six months, a sustained virological response was seen in 51%.

In addition to these three decision problems, the model was also used to explore the level of syringe coverage, OST participation, and HCV treatment required to reduce the prevalence of HIV and HCV amongst the IDUs in a high (Bristol) and low HCV prevalence (Teesside) setting.

Methods

The two infectious diseases were combined in order to evaluate the three decision problems. The combined model simulated the transmission of HIV and HCV infections amongst IDUs, in order to project costs and effects over a 20-year period. Evidence used to populate the model was obtained from the literature, the LJMU effectiveness report, and survey data collected from a high (Bristol) and low (Teesside) HCV prevalence setting. Because of uncertainty in the evidence, a fitting algorithm was used to obtain multiple fits of the model to the epidemiological data for each setting. The model was then used to estimate the impact on HIV/HCV transmission of different intervention scenarios. The base case analysis considered costs to the NHS/PSS and IDU-associated crime. Health outcomes were expressed in terms of quality-

adjusted life-years (QALYs). Future costs and health outcomes were discounted at 3.5% per annum.

Cost-effectiveness evidence summary

1. What level of coverage of needle and syringe programmes (NSPs) is the most effective and cost-effective?

Results from the threshold modelling for decision problem 2 suggest that effective interventions to increase syringe coverage could be cost effective if the associated intervention costs are modest, given a societal cost perspective. The results also suggest that interventions to improve syringe distribution are more likely to be cost-effective in relatively lower HCV prevalence settings compared with relatively higher HCV prevalent areas, as IDUs in the latter setting are more likely to be re-infected. However, for both settings, the modelling results also suggest that although increasing the coverage of syringe distribution or the recruitment rate onto OST is sufficient for controlling HIV, it is insufficient for reducing the prevalence/incidence of HCV. As also found in recent studies from Amsterdam and Wales (unpublished – see Table ES1), our results suggest that multi-faceted interventions (e.g. increased OST recruitment and HCV treatment) are required to achieve substantial decreases in HCV incidence.

Table ES1: HCV incidence amongst current IDUs by level of syringe coverage and whether currently on OST in South Wales IDU cohort [67]

Coverage	**HCV incidence per 100 person years**	**IRR**	**95% CI**
<100% syringe coverage and no OST	10%	1	
>100% syringe coverage and no OST	11%	1.14	0.3-4.2
<100% syringe coverage and OST	6%	0.58	0.1-2.9
>100% syringe coverage and OST	2%	0.17	0.02-1.0

2. What types of NSPs are effective and cost effective?

The quality and availability of the evidence did not permit any cost-effectiveness modelling for this question to be undertaken.

3. Which additional harm-reduction services offered by NSPs are effective and cost effective?

Results from the economic modelling for decision problem 1 suggest that interventions to encourage NSPs users to attend OST programmes are likely to be cost-effective even if the increase in participation rates is only modest. The impact on blood borne viruses may only be modest though unless it is undertaken as part of a group of interventions to reduce their transmission. However, the quality of the evidence demonstrating a positive effect of interventions to increase participation rates is poor (i.e. as per the Strathdee RCT) as stated in the effectiveness report.

The threshold results for decision problem 3 suggest reasonable scope exists for interventions to increase participation rates to HCV treatment to be cost-effective, and to be effective for reducing the transmission of HCV if sufficient recruitment of chronic HCV infecteds is achieved (10% per year or more). However, the evidence to support the effectiveness of such interventions to recruit IDUs is limited.

4. Are NSPs delivered in parallel with, or alongside, opiate substitution therapy (OST) effective and cost-effective?

The quality and availability of the evidence did not permit any cost-effectiveness modelling for this question to be undertaken.

Summary

The scope for NSP-related interventions to be cost-effective is high. This is particularly the case for interventions to increase recruitment rates to OST, as the costs savings associated with successful OST are large, but is also likely to be the case for HCV treatment and increasing the coverage of syringe distribution. However, the main limitation with drawing conclusions with respect to cost-effectiveness is the paucity and quality of the underpinning effectiveness evidence. Lastly, although noticeable decreases in HIV incidence can be achieved with one of these interventions, multi-faceted interventions (possibly including two or more of the interventions modelled here) are needed to substantially decrease the incidence of HCV.

1 Introduction and Objectives

The aim of this report was to undertake economic analyses of interventions linked to needle and syringe programmes (NSPs) for injecting drug users (IDUs), with a view to reducing risky injecting behaviour, viral infection and early death. The analysis presented herein has been developed alongside the 'effectiveness' report produced by Liverpool John Moore's University (LJMU), and should be viewed as a complement to it.

Four broad questions were included in the scope for this project, as set by NICE, and as reported in the effectiveness report:

1. What level of coverage of needle and syringe programmes (NSPs) is the most effective and cost-effective?
2. What types of NSPs are effective and cost effective?
3. Which additional harm-reduction services offered by NSPs are effective and cost effective?
4. Are NSPs delivered in parallel with, or alongside, opiate substitution therapy (OST) effective and cost-effective?

1.1 Determining the relevant NSP-related treatment interventions to be evaluated

The four questions set by NICE in the scope document were considered to be 'broad', in so much that collectively they covered a multitude of different potential interventions to evaluate. Thus the first step in terms of performing an economic evaluation, or evaluations, was to identify the relevant decision problems (that is the interventions to be evaluated, their comparators and the relevant IDU populations). Three main factors were used to guide these

considerations: 1) the relevance of the intervention at hand to current UK NSP-related practice 2) the availability and access to existing NSP-related models and associated datasets, given project time constraints and 3) the results from the systematic review of the clinical literature (given the premise that if evidence of an intervention's effectiveness did not exit, or was of poor quality, it would be difficult to estimate its cost-effectiveness in to any meaningful degree).

1.2 The availability and access to existing NSP models and associated data sets

Irrespective of the precise interventions to be evaluated, it was understood at the beginning of the project that modelling NSP-related activities is a relatively complex task, given that HIV and HCV are infectious diseases, and that co-infections are possible. Indeed, the scope for this project correctly recognised this to be an important issue and stated that any modelling should therefore be 'dynamic' in its construction. Thus, an overriding approach with respect to modelling the cost-effectiveness of NSP-related interventions, was to utilise already published infectious diseases models, rather than spending considerable time reinventing the wheel. More specifically, the approach taken was to bring together two models already developed by Vickerman, one relating to HCV infection in IDUs and the other relating to HIV infection in IDUs.

The decision to 'join' pre-existing models of infection was an important consideration for the purposes of this modelling exercise in so much that it bounded the type of NSP-related interventions that could be evaluated; those that were designed to prevent HIV / HCV infection rather than say, bacterial

infections at the injection site. It also meant that the systematic review of the clinical literature needed to produce evidence that interventions affected specific outcomes (eg. the risk of sharing needles or the risk of overdose), which were already inbuilt into the model rather than others (eg. syringe use – which alone presents no obvious risk of further viral infection if a person reuses their own injecting equipment, and is not a useful outcome as it is superseded by risk of sharing needles).

Joining these specific models also meant that interventions for certain high risk IDU cohorts, such as the homeless and those in prison, were excluded from the analysis. This was because the models were not designed with these cohorts in mind and the datasets required to inform any potential alterations, were not readily available.

Consideration was given to the importance of modelling the prevention of hepatitis B infection through changes in risky injecting behaviour, as set out in the scope document. However, provisional examination of the evidence suggested that the incidence of HBV infection in IDUs in the UK is relatively low and stochastic in nature. Thus, the costs and benefits of preventing HBV infection are difficult to assess, and were excluded from the model. Note that the model was not suited to evaluating interventions to prevent local bacterial infections, thus these interventions were excluded from consideration.

1.3 Results from the systematic review of the clinical literature

The results from the initial systematic literature review identified 22 primary studies (see Appendix 3 of this report). Later in the assessment process a

further 3 studies were identified, leaving a total of 25 effectiveness studies. In line with the effectiveness report, they were broadly categorised as either considering the effectiveness of: different levels of coverage to sterile injecting equipment, types of NSP, accessibility to NSPs and facilitating entry to drug treatment once at a NSP. A detailed critique of each of these studies is provided in the effectiveness section of the report. At a later stage in terms of putting this report together, a 23rd (unpublished) study by Wilkinson was identified; a study that evaluated the effectiveness of an intervention to increase recruitment to HCV antiviral treatment via NSPs. Even further into the project, the systematic reviewing team identified two further studies. While they were identified too late to be formally included in the this report, neither study was judged to have been a significant omission [1, 2]. Thus, 25 studies were identified in total, of which 23 were considered for inclusion in the economic analysis

Overall, the 23 studies were considered to be of very poor quality in terms of their design (only 4 were based on RCTs; the remaining 18 were either cross-sectional or cohort studies) and not particularly useful in terms of identifying interventions to evaluate. The most common problem was that most of the studies did not evaluate interventions per se, rather they assessed relationships between variables. For example, the study by Bluthenthal et al. [3], assessed the relationship between syringe coverage and risk taking outcomes such as sharing injecting equipment, but said little about interventions to increase coverage. Studies assessing the relationship between location of NSP and usage also fell within this category of study eg.

Miller et al 2002. Moreover, where attempts were made to evaluate specific interventions, they were often poorly described. A number of non-UK studies examined whether pharmacy sales of sterile injecting material, was related to improvements in risky injecting behaviour. However, the private sale of such materials was not considered to be an appropriate topic for this project because free distribution of syringes/needles is available at many pharmacies in the UK. Lastly, while a number of studies suggested differences in terms of needle reuse, it was not clear how this could result in reduced rates of viral transmission, for reasons previously described.

Consideration of the evidence covered in the effectiveness review suggested that only one study could be readily incorporated into an economic evaluation. The study by Strathdee et al, was a US-based RCT that assessed the effectiveness of a specific method of encouraging IDUs, who expressed an interest in starting OST, to enter appropriate drug treatment programmes. More specifically, IDUs attending a NSP in the control arm, who expressed an interest in starting OST, were literally given appointment details for a drug treatment programme, but no specific 'encouragement' to attend the meeting. Whereas IDUs randomised to receive the 'strengths-based management programme', were assigned case managers to assist clients in setting and achieving treatment goals, with a view to increasing participation rates in OST programmes. The report for the RCT states that the duration and frequency of case-management contacts were case driven, and that additional services were offered to clients such as transport to and from the treatment centre, child care and social services. Case managers also underwent 3-days of

training. However, few useful details with respect to actual resource consumption for either the intervention or control arms are reported. Outcomes were recorded as the number of people attending an initial OST meeting within 7-days of referral from the NSP (intervention 40% vs control 26%). No data were collected past this point.

The Bluthenthal 2007 [3] study assessed the association between syringe coverage and a number of risk behaviours such as receptive risk sharing. While it therefore did not evaluate a technology *per se*, the decision was taken to conduct a threshold analysis to assess how costly programmes to increase syringe coverage could be, given the demonstrated associations with syringe sharing, for cost-effectiveness to be achieved. Although not explicitly modelled, possible strategies that could increase syringe coverage could include opening NSPs for longer hours or using mobile vans or vending machines to increase access. To make the analysis more relevant, data from a survey of IDUs in seven English cities was analysed to obtain equivalent data on the association between syringe distribution coverage and syringe sharing. This analysis also explored what impact could be achieved from increasing an IDU's syringe coverage and was undertaken using the same model as for assessing the cost-effectiveness for the intervention described in the Strathdee RCT [4].

In addition to these two studies from the effectiveness review, the unpublished study by Wilkinson et al. was also incorporated into the economic analysis, again using a threshold approach. This study looked at whether the coverage

of HCV antiviral treatment could be improved through the provision of a specialist clinic at an NSP/drug agency. Although not a RCT, the study strongly suggested that the NSP based intervention increased the rate at which HCV infected IDUs entered HCV treatment from negligible levels up to about 5% per year. The increase in coverage was thought to be due to basing the service at the IDU's regular point of contact, and because the specialists running the clinic were not averse to IDUs obtaining HCV treatment.

From the four questions outlined in the scope document, the following three decision problems were identified:

Decision problem 1: Is the intervention to increase participation in OST programmes, as broadly described in Strathdee et al, cost-effective compared with no specific encouragement to participate, in IDUs expressing an interest in receiving treatment for their injecting drug addiction?

Decision problem 2: What additional cost would be acceptable if it were possible to increase sterile syringe coverage for IDUs?

Decision problem 3: What additional cost would be acceptable if it were possible to increase the recruitment of HCV infected IDUs onto HCV treatment through existing NSPs, as described in the unpublished study by Wilkinson et al.

Decision problem 2 was undertaken in an attempt to answer question 1 in the scope, whereas decision problems 1 and 3 fall under question 3 because both are NSP based interventions designed to reduce the harms experienced by IDUs, and may reduce the transmission of blood-borne viruses. In addition, because of the current low provision of HCV treatment for IDUs and the debate over its effectiveness for IDUs because of re-infection, it was decided that modelling its likely impact and cost-effectiveness for IDUs should be a priority because it has not been considered before. Decision problem 1 also has relevance to question 4 but does not consider the possible added benefit of opiate substitution therapy being given at an NSP - there was insufficient data to do this. Insufficient data was also available to answer question 2 and so our analyses focussed on estimating the incremental impact/cost-effectiveness assuming a baseline of what is currently undertaken in England.

In addition to these decision problems, the model was also used to estimate the level of syringe coverage and other interventions required to reduce the prevalence of HCV amongst the IDUs in these two settings. This analysis was undertaken to address Question 1 but did not incorporate cost data because of its exploratory nature.

2 Methods

2.1 The cost-effectiveness evaluation process

Once these three decision problems had been identified, a five stage process was used to produce estimates of cost-effectiveness. First, the existing economic evidence was reviewed in order to assess its relevance and

usefulness to the decision problems at hand. Second, the model structure and clinical data required to populate the model were assembled, largely by combining and adapting two previously published infectious diseases models. This model was fit to epidemiological data from Teesside and Bristol to represent a low and high HCV prevalence setting. Third, the model was run to report a trace of the results by health state for each treatment option for each setting (that is, the number of people in each health state / compartment per time step). Fourth, costs and utilities were attached to the trace. Lastly, expected costs and QALYs were reported for each of the strategies and incremental cost-effectiveness ratios (ICERs) reported and sensitivity / threshold analyses undertaken.

The base case analysis was performed from a societal perspective, in so much that NHS / PSS and the costs of crime IDU-associated were considered. Productivity costs were not included in the broader perspective as there was no evidence to suggest that employment status changes as a result of OST treatment (Godfrey 2007). Future costs and benefits were discounted at 3.5% per annum, over an arbitrarily chosen time horizon of 20-years. All health care costs were up-rated to 2007 prices using the Hospital and Community Health Services pay and prices index. Non health care costs were up-rated to 2007 prices using the retail price index.

2.2 Existing economic evidence

Results from the systematic literature review undertaken by LJMU identified 13 published economic evaluations. They are critiqued in full in the effectiveness report. However, broadly speaking, they were judged not to be

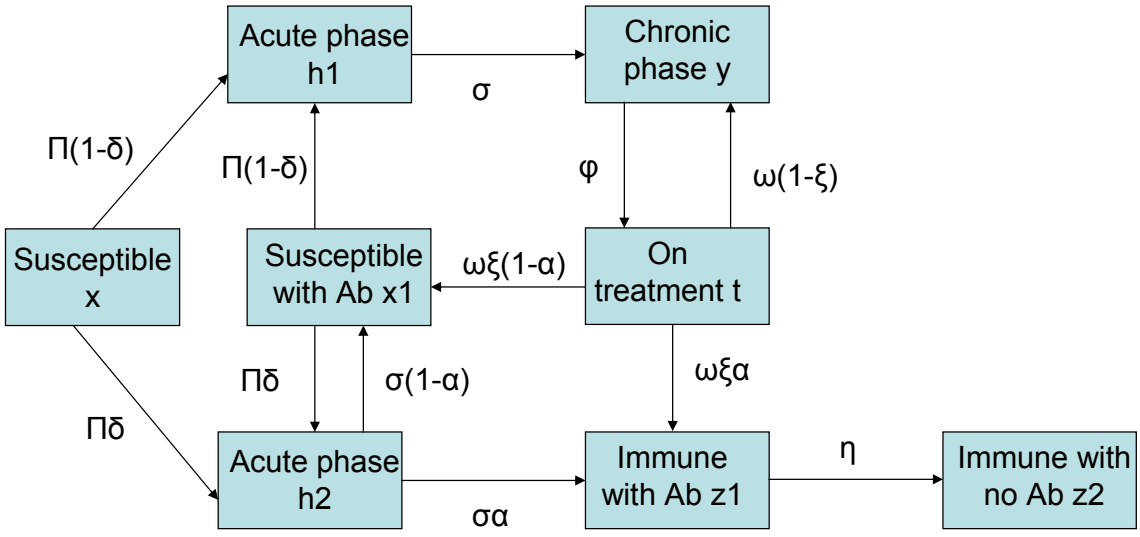
particularly useful with respect to contemporary UK (NHS) decision-making and the scope for this project, a conclusion also reached in the associated effectiveness report. First, none of the economic evaluations contained UK-based analyses meaning that the applicability of their results for the purposes of NICE decision-making was questionable. Second, 11 of the 13 evaluations focused on interventions to reduce HIV infection, rather than HCV infection, or both. Lastly, none of the evaluations expressed health benefits in terms of quality-adjusted life-years (QALYs).

2.3 Model description

A model of HCV and HIV transmission was developed to simulate the transmission of HIV and HCV amongst IDUs, and to project the impact of OST or NSP interventions. The HCV transmission model is based on the model published in a previous study by the author [5], but has been adapted to incorporate HCV treatment and recent evidence suggesting that IDUs who resolve their infection or are treated can be susceptible to reinfection [6-10], and has the structure shown in Figure 1. The model assumes that IDUs enter an acute phase of infection once they are infected, and then either resolve their infection after a number of months or progress to chronic infection. A proportion of those that resolve their infection are assumed to become immune, and the remainder become susceptible again, but with a positive antibody response. Those that develop chronic infection remain infected. All infecteds develop an antibody response during their acute phase. As before, the model includes three behavioural subgroups of IDUs depending on whether they do not share, or share with a low or high frequency, and is adapted so that it simulates the transmission of HCV over time, with two

groups for those that have just started injecting and those that have been injecting for longer [5]. Because of this, the model now includes a parameter for the rate at which they cease injecting or die due to overdose, and also a term for IDUs leaving due to HIV and non-HIV related mortality. The model allows for new IDUs to have a different frequency of syringe sharing. The equations and a more detailed description of the HCV model are included in appendix 1.

Figure 1: Flow diagram for HCV transmission model. Arrows portray possible transformations of susceptible or infected IDUs, and the parameters next to these arrows are the rate of flow per capita between these states



The HIV transmission model assumes the same behavioural sub-groups as the HCV model, and assumes that once a susceptible is infected they progress to an acute high viraemia phase of infection, following which they progress to a longer stage of low viraemia, a short period of high viraemia, and then progress to full blown AIDS. The model also allows for HIV infected IDUs to start HAART, with recruitment rates from the asymptomatic, pre-AIDS

and AIDS stages. HAART is assumed to increase the duration to AIDS and HIV-related death, and reduces the transmission probability for that person.

The focus of the study was to look at the impact of interventions aiming to reduce injecting risks, and so the model did not simulate the sexual transmission of HIV. The equations and detailed description of the model are in Appendix 1.

The model also incorporates the possible effect of different interventions, such as OST and NSP and combinations there of. However, because all IDUs in Teesside and Bristol seem to have contact with some form of syringe distribution, the NSP category was defined as those IDUs that have greater than 100% syringe coverage (defined as the number of syringes/needles they obtain for their own use per unit time divided by the number of injections they have in the same time period). After a certain time point, the model assumes that IDUs are recruited on to OST and/or achieve a certain level of syringe coverage at a specified recruitment rate. They move to an equivalent model category specific to their infection state and syringe sharing behaviour, but with the assumption that their syringe sharing rate reduces by a specific ratio depending on whether they are on OST, have a certain level of syringe coverage or both. The IDUs are also assumed to have a lower death rate while on OST, but leave OST at a specified rate dependent on the retention rate in that setting and then return to their corresponding non-OST model category. IDUs are also assumed to move between the different levels of syringe coverage.

2.4 Data used for model analysis

Biological data used to parameterize the model was obtained from the literature, and the estimates used in the model analysis with their uncertainty bounds are shown in Table 1. Values within these uncertainty bounds were used in this analysis.

Table 1: Model parameters for fitting algorithm

Epidemiological model parameter		**Bristol**	**Teesside**
HCV prevalence overall		64.9% (57.8-71.4%)	26.8% (20.7-33.5%)
HCV prevalence amongst injectors <=3 years		40.0% (19.1-63.9%)	13.6% (5.2-27.4%)
HCV prevalence amongst injectors >3 years		67.6% (60.3-74.3%)	30.5% (23.4-38.4%)
HIV prevalence		1.0% (0.2-2.9%)	0% (0-1.8%)
Behavioural model parameter			
Duration inject drugs	New IDUs (injecting <=3yrs)	5-10yrs	0.5-1*Bristol durn
	Older IDUs (Injecting >3yrs)	20 yrs	0.5-1*Bristol durn
Non-HIV mortality rate [11, 12]		1.5%	1.5%
Percentage of IDUs that share injecting equipment		>70%	>35%
Of those IDUs that syringe share:			
Percentage that share 1-4 times in last 4 weeks		62.5%	81.4%
	Frequency of syringe sharing	2.1	1.8
Percentage that share >4 times in last 4 weeks		37.5%	18.6%
	Frequency of syringe sharing	11.7	10.0
Intervention parameters			
Percentage with coverage <100% and not on OST		36.4%	14.0%
Percentage with coverage >100% but not on OST		18.2%	8.5%
Percentage with coverage <100% but currently on OST		22.7%	44.0%
Percentage with coverage >100% and currently on OST		22.7%	33.5%
Average rate recruited onto OST per month¥		0.039	0.084
Average rate leave OST per month¥		0.051	0.024
Ratio decrease in overdose death rate while on OST		10 [13, 14]	
Average rate achieve 100% syringe coverage per month¥		0.027	0.055
Average rate leave 100% syringe coverage per month¥		0.049	0.073
Proportion of IDUs that have been tested for HCV [47]		79%	50%
Proportion of IDUs that have received a HCV test per year (varies hugely [15])		27% (fit model to data above)	10% (fit model to data above)
Ratio of mean syringe sharing rate if:			
Coverage <100% and not on OST		2.05 (1.21-2.89)	
Coverage >100% and not on OST		0.74 (0.49-1.19)	
Coverage <100% and on OST		0.84 (0.43-1.05)	
Coverage >100% and on OST		0.61 (0.36-0.86)	
HIV biological model parameter		**Value used**	**Data source**
Percentage of IDU HIV infections acquired in the UK		52%	[16]
HIV transmission probability per syringe sharing event		0.14-1.41%	[17-19]
Cofactor increase in HIV transmission probability during			
	Initial period of high viraemia	7	[20-24]
Pre-AIDS period of high viraemia		3	[24]

Duration of initial period of high viraemia in months	1.5	[23]
Duration of pre-AIDS period of high viraemia in months	6 mths	[24]
Without HAART - median duration till AIDS	11 yrs	[25, 26]
- median survival time with AIDS	1 yr	
With HAART compared to without HAART- duration till AIDS	3 times	[27-29]
- median survival time from AIDS	4 times	
Coverage of HIV infected IDUs on HAART in the UK	~20%	[16, 30]
Recruitment rate on to ART during pre-AIDS HIV infection	1.1% per year	Fit to HAART prevalence
Recruitment rate on to ART during AIDS	50% within a year	Assumption
Factor decrease in transmission probability while on ART	V.low – assume 0.02	[31-36]
HCV biological model parameter	**Value used**	**Data source**
Ratio of HCV transmission to HIV transmission probability	7.5-15	Little data [5]
Duration of acute phase of infection in months	3-24mths	[5, 37, 38]
Proportion of HCV infecteds that resolve infection	26% (20-50%)	[39]
Proportion of resolved/treated infecteds that become immune	50-100%	[6-8, 10, 40]
Percentage of HCV chronic infected IDUs that have had HCV treatment	<4.8%	[41, 42]
Proportion of HCV positive IDUs that enter treatment	1.6-9% of those newly tested	[41], and fit to data in row above
Duration of treatment	9 months	[42, 43]
Percentage of treated infections cured (includes compliance)	52%	Combined result of studies [10, 42-46]

In contrast, the behavioural and epidemiological data for Bristol and Teesside was collated from two survey data sets, one of which has already been published [47]. The first data set was part of a multi city cross sectional survey undertaken in 2004 (including both study sites) that wanted to assess whether geographical differences in HCV prevalence could be explained by differences in behaviour [47]. The second survey is still unpublished and used respondent driven sampling and HCV RNA testing in addition to antibody testing to explore the transmission of HCV in Bristol. These data sets were analysed in SPSS to gain a greater understanding of the drivers of HCV transmission in both settings, to explore the level and effectiveness of current

intervention activities, and to obtain estimates for the behavioural and epidemiological parameter values needed for the model.

Some of the data collated for each setting is shown in Appendix 2, and gives a number of insights. The two settings have contrasting HCV prevalence's, with Bristol being quite high (65%) and Teesside being quite low (27%), but both have negligible HIV. Current IDUs in either setting have been injecting for on average 10 years, and although data from elsewhere suggests that these IDUs are likely to inject for 10-20 years on average, there is also likely to be a large number of IDUs that inject for one year or less (Sweeting et al. unpublished data). The frequency of injecting in both settings is on average two or three times a day, and reported syringe sharing is high with 15-32% of IDUs sharing syringes in the last four weeks (>50% ever) and >50% sharing some type of injecting equipment in the last 4 weeks. Despite this risk behaviour, there is a high coverage of syringe distribution in both settings, with on average over 100% of injections being covered by a new syringe and only 25% of IDUs having less than 50% coverage. The majority of IDUs are currently on OST (50-75%), with the duration on OST generally being 1-2 years, and these IDUs generally have a lower frequency of injecting and syringe sharing, although both are still prevalent. The main differences in risk behaviour between the two settings are that IDUs in Teesside have been injecting for a shorter time, so they may have a shorter injecting duration.

The behavioural data collated from these two surveys and other sources was used to produce the model parameter values in Table 1. Because of the

comparability of methods and survey instruments used, the multi-site survey was the main data source used to obtain parameter values for Bristol and Teesside. Ranges were assigned to certain key behavioural parameters either because of their importance in determining the impact of interventions or because of the likely biases or uncertainties normally associated with them. These include such things as the proportion of IDUs that syringe shared in the last four weeks, which was given a range depending on the proportion of IDUs that report sharing syringes or other injecting paraphernalia in the last 4 weeks or ever, the duration IDUs inject for, and intervention parameters such as the relative frequency of syringe sharing while on OST or with over 100% syringe coverage.

Other data needed to parameterise the model include such things as the recruitment rate of HIV infected IDUs on to HAART or HCV infected IDUs on to HCV treatment. For HIV, data on the proportion of HIV infected IDUs on HAART (~20%) from the HPA [16, 30] was used to estimate the HAART recruitment rate for IDUs in the asymptomatic phase of infection, while assuming that 50% of AIDS cases are recruited on to HAART per year. This gave a recruitment rate of 1.1% per year. For the treatment of HCV chronic current IDUs, data from two sources suggested that a low proportion of HCV infected IDUs referred to specialist hepatology clinics end up having HCV treatment (1/61) [41], and a low proportion have been referred for treatment in the past (6/124) [42]. In addition, not all IDUs are tested for HCV, with 79% and 50% having been tested at some point in Bristol and Teesside. To derive the HCV testing rates, a simple model was fit to the prevalence of testing in

Bristol and Teesside. The model then assumed that a proportion of the tested chronic HCV infected IDUs were then recruited on to treatment. This ranged from 1.6% (1/61) to agree with the data from Irving et al., to 9% (model fit) to agree with the prevalence of previous treatment from Jack et al. All IDUs recruited onto HCV treatment were assumed to receive pegylated interferon alpha plus ribavirin, and the treatment effectiveness was derived by collating data from a number of studies undertaken amongst IDUs (Table 1).

2.5 Model fitting

Because of uncertainty in these behavioural and biological parameters, a fitting algorithm was used to obtain multiple fits of the model to the epidemiological data for each setting. The algorithm involved a number of steps: Firstly, 100 parameter sets were sampled from the HCV biological parameter uncertainty bounds and the HIV transmission probability. For each of these parameter sets, and separately for Bristol and Teesside, 100 behavioural parameter sets were sampled from the parameters with ranges assigned to them in Table 1. The model was run for each of these 10,000 parameter sets until the HCV prevalence reached an endemic level and the HIV epidemic had progressed for 30 years. If the projected HCV and HIV prevalence estimates (overall, <=3 and >3 years injecting) were within the confidence limits of the prevalence estimates in Table 1 for that setting then that model simulation was kept as a possible fit. Any possible fit for a particular setting that also had a possible fit for the other setting with that biological parameter set was kept as a model fit and all others were rejected. This was done because we wanted to only accept possible biological parameter combinations that are consistent with the HCV /HIV epidemics in

both settings. In total, 734 model fits were obtained for Bristol and 726 for Teesside. The model fits projected an average HCV prevalence of 28.1% (19.7-33.3%) for Teesside and 62.0% (58.0-69.3%) for Bristol. Table 2 compares the ranges used for the inputs in the uncertainty analysis and the mean and range of parameter values that gave model fits to the epidemiological data.

Table 2: A comparison of the prior and posterior parameter ranges of the model fits

Model parameter	Bristol			Teesside		
	Range used in uncertainty analysis	Mean of fits	Range of fits	Range used in uncertainty analysis	Mean of fits	Range of fits
Rate stop injecting drug use per year if injected for <=3 years	0.10-0.20	0.14	0.1-0.2	0.10-0.40	0.21	0.12-0.39
Rate stop injecting drug use per year if injected for >3 years	0.040-0.067	0.054	0.04-0.067	0.040-0.13	0.08	0.05-0.13
Percentage that do not share syringes	0.15-0.30	0.23	0.16-0.30	0.30-0.60	0.52	0.35-0.60
Ratio of mean syringe sharing rate:						
Coverage <100% and not on OST	1.0-3.0	1.84	1.0-3.0	1.0-3.0	2.0	1.2-3.0
Coverage <100% but on OST	0.35-1.2	0.74	0.39-1.2	0.35-1.2	0.73	0.35-1.1
Coverage >100% and not on OST	0.41-1.3	0.83	0.41-1.2	0.41-1.3	0.87	0.50-1.3
Coverage >100% and on OST	0.22-0.93	0.62	0.22-0.93	0.22-0.93	0.62	0.33-0.89
Assortative mixing between IDUs of different syringe sharing rates	0.10-0.50	0.29	0.11-0.50	0.10-0.50	0.29	0.10-0.50
Assortative mixing between IDUs of different duration injecting	0.10-0.50	0.28	0.10-0.50	0.10-0.50	0.34	0.11-0.50
Rate recruit on to HCV treatment per month for baseline	0.0043-0.012	0.0081	0.0045-0.012	0.0016-0.0090	0.0051	0.0017-0.0088
HIV transmission probability per syringe sharing incident	0.001-0.0069	0.0013	0.0010-0.0022	0.001-0.0069	0.0014	0.0010-0.0022
Factor difference between HIV and HCV transmission probability	7.5-15	9.76	7.8-14.9	7.5-15	9.5	7.8-14.9
Rate leave acute phase in months	0.056-0.33	0.16	0.06-0.28	0.056-0.33	0.15	0.060-0.28
Proportion resolve HCV infection	0.20-0.50	0.32	0.22-0.45	0.20-0.50	0.33	0.22-0.45
Proportion immune to HCV reinfection after resolve infection	0.50-1.0	0.70	0.51-0.89	0.50-1.0	0.71	0.51-0.89

Table 2 shows that for most parameters, the full uncertainty range was used in the simulations that fit the epidemiological data from Teesside and Bristol.

The main exception to this was the HIV transmission probability that had a much reduced upper bound for the model fits – 0.0022 per syringe sharing incident instead of 0.0069. This was required to obtain the low HIV prevalence observed in these two settings. The other parameters that had reduced ranges in the model fits were the: Percentage that do not share syringes in Teesside, the ratio of the mean sharing rate with different levels of intervention contact, the proportion that resolve their HCV infection, and the proportion that are immune once they resolve their HCV infection.

Many of the variables in Table 2 were correlated in the model fits, with some being higher if others were lower and vice versa. However, only a few were positively correlated to any noteworthy degree and these were all from the Teesside model fits (with a correlation coefficient>0.3):

1. Percentage of IDUs that do not share syringes and the ratio of the mean syringe sharing rate if an IDU has >100% coverage but not on OST
2. Percentage of IDUs that do not share syringes and HIV transmission probability
3. Ratio of the mean syringe sharing rate if an IDU has >100% coverage and on OST and the ratio of the mean syringe sharing rate if an IDU has >100% coverage but not on OST

The associations in 1 and 2 are easy to understand in that if the percentage of IDUs that do not share is high then there will tend to be less HIV/HCV and so the HIV transmission probability and/or ratio of the mean syringe sharing rate if an IDU has >100% coverage but not on OST are greater to compensate. Association 3 is harder to understand but may be linked to 1. Similarly, only a

few were negatively correlated to any noteworthy degree and these were also all from the Teesside model fits (with a correlation coefficient<-0.3):

4. HIV transmission probability and the rate infected IDUs leave the HCV acute phase
5. Ratio of the mean syringe sharing rate if an IDU has <100% coverage and not on OST and the ratio of the mean syringe rate if an IDU has >100% coverage but not on OST

Association 5 is easy to comprehend that is one ratio is high then the other needs to be lower to give the correct HIV/HCV prevalences, whereas association 4 may be due to the HIV and HCV transmission probabilities being related by the 'factor difference between HIV and HCV transmission probability', If the HCV transmission probability is high then the rate at which people leave the acute phase has to be lower to reduce the HCV prevalence. These correlations suggest that the uncertainty in the output projections could be reduced if the uncertainty in some of these parameters could be reduced.

2.6 Intervention impact analysis

In line with the outlined decision problems, the model fits for each setting were used to evaluate: 1) the impact of increasing the recruitment of IDUs on to OST through existing NSPs; 2) increasing the coverage of syringe distribution (coverage being defined as the number of syringes they obtain divided by the number of injections an IDU has per unit time, which will be greater than 100% if they obtain more syringes than they inject per week); and 3) increasing the recruitment of HCV infected current IDUs onto HCV treatment through existing NSPs. These scenarios are described in more detail below.

2.7 Increases in syringe distribution coverage

It is generally believed that increasing the availability of syringes to IDUs will reduce their level of needle/syringe sharing and should reduce the transmission of blood borne viruses. However, although there are data showing that the initiation of syringe distribution interventions reduces risk behaviour and HIV transmission [48-51], there are very little equivalent data for HCV [52, 53], and even less on the possible effects of different levels of syringe coverage on injecting risk behaviour [3, 54-56] or HIV transmission [57]. However, two recent studies have shown that IDUs with higher levels of syringe coverage are likely to share syringes less [54] and syringe distribution interventions with less restrictive distribution strategies are likely to achieve higher syringe coverage levels than NSPs with more restrictive policies [3]. Although NSPs in the UK generally have a fairly unrestricted needs based distribution strategy, the results of these studies gave sufficient reason to investigate the possible increased impact that could be achieved if other NSP-related strategies could increase the coverage of their syringe distribution. Possible strategies to achieve this could include opening NSPs for longer, or seven days a week, or introducing vending machines in order to ensure ensuring that IDUs have easy access to NSPs, or possibly counselling IDUs on the importance of not re-using syringes.

To ascertain how any increases in syringe coverage may decrease the syringe sharing of IDUs in Teesside or Bristol, the data from all settings in the multi-site study was used to explore the relationship between an IDU's level of syringe coverage and their frequency of syringe sharing. Figure 2 shows the strong relationship between these variables in this study, with IDUs that have

a syringe coverage of between 0 and 50% having four times the frequency of syringe sharing of IDUs with >200% coverage.

Because of its significance as an intervention target, and because the level of syringe sharing is fairly constant at syringe coverages >100%, an IDU's level of syringe distribution was defined in the model as whether they had a syringe coverage of less than or greater than 100%. This was assumed to increase or decrease the frequency of syringe sharing by a cofactor depending on whether they were also currently on OST. This cofactor for each intervention category was estimated by comparing the average syringe sharing rate in this group for the whole multi-site study with the overall average syringe sharing rate (Figure 3). The proportion of the IDU population in each of these coverage and OST groups was determined from setting specific data from the multi-site study, and is shown in Table 1.

The analysis modelled a number of scenarios of how a hypothetical intervention may affect the proportion of IDUs with greater than 100% syringe coverage. It was assumed that the intervention increased the recruitment rate into the >100% coverage class, or reduced the rate at which they leave the high coverage class. The parameter values for these scenarios are shown in Table 3.**Error! Reference source not found.**

Figure 2: Relationship between syringe coverage and and IDUs frequency of syringe sharing in seven cities in the UK

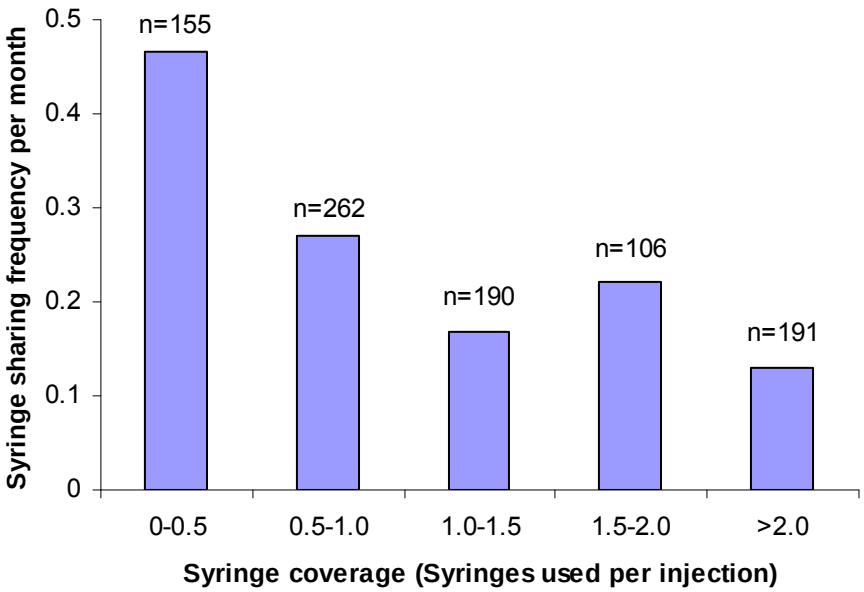
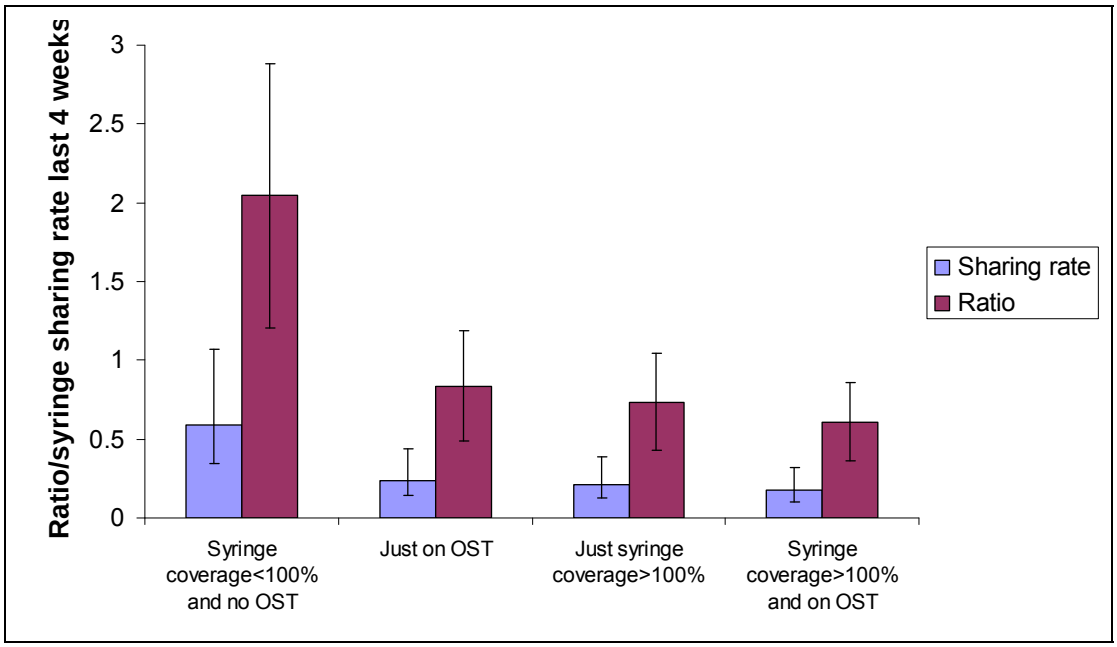


Figure 3: Relationship between syringe sharing frequency, and ratio compared to mean sharing frequency (0.29 in last 4 weeks), for different levels of intervention participation in seven cities in the UK



2.8 Increasing the recruitment of IDUs on to OST through existing NSPs

The other intervention modelled in this analysis was the use of counselling and active case management to improve the recruitment onto OST of IDUs

attending NSPs, for IDUs expressing an interest in drug treatment. The data used to model the possible impact of this intervention is from a US randomised trial that compared the proportion of IDUs attending their initial treatment meeting if a basic referral system was used or strength based case management was used [4]. The study found that the proportion of referred IDUs that attended their initial treatment meeting (within 7-days) increased from 26% to 40% (a 53.8% relative increase). In this analysis, we assumed that undertaking the intervention in Bristol or Teesside would increase the overall recruitment rate onto OST by a similar amount to the 53.8% increase observed in the trial [4]. This level of increase is likely to be an upper bound for the possible intervention effect, and will be dependent on the proportion of OST patients that are referred through NSP and the likelihood that IDUs initiate OST following their initial treatment meetings. For this reason, a number of other less optimistic scenarios were also modelled where the OST recruitment rate was assumed to increase by smaller amounts. In addition, one other scenario was also modelled to see what impact could be achieved if the recruitment rate on to OST was much greater. All IDUs that are recruited onto OST were assumed to have the same ratio decrease in their syringe sharing rate as shown in Table 1 and were assumed to stop OST at the rates shown in Table 1. The scenarios modelled for this intervention scenario are shown in Table 3.

Table 3: Intervention scenarios for modelling impact projections

Scenario	% increase in OST recruit rate	% increase in 100% coverage recruitment rate	% decrease in 100% coverage leaving rate	% of HCV infected IDUs recruited on to treatment each year
Interventions to increase recruitment to high syringe coverage				
Low	0%	12.5%	0%	Baseline level†
Medium	0%	25%	0%	Baseline level†
High	0%	50%	0%	Baseline level†
Very high	0%	100%	0%	Baseline level†
Intervention to reduce rate IDUs leave high coverage group				
Low	0%	0%	12.5%	Baseline level†
Medium	0%	0%	25%	Baseline level†
High	0%	0%	50%	Baseline level†
Very high	0%	0%	75%	Baseline level†
Intervention to increase recruitment on OST				
Low	13.5%	0%	0%	Baseline level†
Medium	26.9%	0%	0%	Baseline level†
High	53.8%	0%	0%	Baseline level†
Very high	100%	0%	0%	Baseline level†
Intervention to increase recruitment onto HCV treatment				
Medium	0%	0%	0%	5%
High	0%	0%	0%	10%
Multi-faceted interventions				
Just OST‡	108%	0%	0%	Baseline†
Just NSP	0%	100%	75%	Baseline†
OST+NSP‡	108%	100%	75%	Baseline†
All interventions				
Low*	53.8%	50%	50%	10%
High‡	100%	100%	75%	10%

† baseline level of recruitment is variable but is assumed to be less than 0.9% (10% tested per year and <9% of these are treated) per year in Teesside, and 2.43% in Bristol (27% tested per year and <9% of these are treated). ‡These interventions also assume a 75% lower rate at which IDUs leave OST. *This intervention also assume a 50% lower rate at which IDUs leave OST.

2.9 Increasing the recruitment of HCV infected IDUs onto HCV treatment through existing NSPs

The current coverage of HCV treatment for HCV infected current IDUs is very low with very few IDUs being referred to specialist clinics [43] and few of them being treated [41, 42]. However, recent data has shown that over 50% of treated IDUs can achieve sustained virological response [10, 42-46], and limited data suggest that the rate of re-infection may be low [7, 10, 58]. In an attempt to increase the recruitment of current IDUs on to HCV treatment, a recent unpublished study from London [43] started a monthly outreach clinic in their Addiction Unit (includes a syringe distribution point and other services) where a consultant hepatologist and senior nurse reviewed clients who expressed an interest in antiviral treatment. Over each year of the two year study, about 5% of the chronically HCV infected IDUs entered treatment. This is much higher than the low rates of HCV treatment that occur currently and suggests that basing this type of a service at an NSP could be an effective method of increasing uptake. To simulate the possible impact and cost-effectiveness of undertaking this additional service at an NSP, we modelled two scenarios where the recruitment rate of infected IDUs on to HCV treatment increases to 5% and 10% per year (Table 3).

2.10 Resource use and costs

The infectious disease model simulated movements between a variety of virus free, HIV- and HCV- related health states, as well as taking into account whether people were current IDUs or were no longer injecting. The next step in the modelling process was to assign costs and effects to the various health states, in order to estimate the cost-effectiveness of the various strategies.

Three categories of cost were defined:

- The input costs of encouraging IDUs to attend drug treatment programmes (i.e. for the intervention to increase recruitment to OST)
- The health care costs associated with HIV / HCV infection
- The health care and broader costs associated with IDUs and successful / unsuccessful OST.

No useful published data on the resource use and costs of encouraging IDUs to attend drug treatment programmes could be identified. Moreover, the Strathdee RCT [4] says nothing about the resources consumed in either the treatment or control arms of the trial. However, data provided by the NTA suggests a national median (rather than mean) cost of £30 per hour with a three tier provider (ie. excluding pharmacy exchange schemes). It was assumed that the strengths based management model to increase attendance at the initial OST meeting, as described in the Strathdee RCT [4], would require a two hour session with an appropriate councillor (Table 4). An arbitrary additional cost of £15 was also added in to cover the cost of transport to the initial treatment meeting (as the RCT reported this to be the most important predictor of attendance to the initial meeting). The cost of this intervention was applied to all people who were not on OST in each year, who expressed an interest in receiving OST; assumed to be 20% of people not on OST per year. Although it is acknowledged that not all people who express an interest in OST, and arrange an initial meeting, attend this initial meeting

(81% in the Strathdee RCT), it was still assumed that a cost was incurred for these people.

The annual health care costs of OST (including drug and programme costs) were taken from a Dutch RCT published in 2005 [59]. The results from this trial produced a mean cost per person of 1,412 Euros for the methadone only treatment arm, in 2001 prices. This was taken to be equivalent to £1,482 in 2007 prices (using an exchange rate of £1 = Euros 1.25); see Table 4.

The health care costs associated with HIV infection, at various stages of disease, were taken from the most recent National Prospective Monitoring Service reports – a UK based observational cohort study designed to assess HIV-related resource use and costs – and arguably the best source on information on the cost of HIV infection in the UK [60]. The health state specific costs of HCV infection at various disease stages were taken from a 2007 HTA report Shepherd et al 2007 [61], commissioned for NICEs Technology Appraisals Programme, assessing the use of pegylated interferons for mild HCV (and its associated NICE Technology Appraisal Guidance). However, the model by Shepherd et al. subdivided chronic infection into a number of health states (including mild, moderate and cirrhotic disease), whereas this model only contained a single health state for this stage of disease (chronic HCV infection). Thus, a single weighted average cost was calculated by approximating the amount of time a person with chronic HCV is likely to spend in the various stages of chronic infection. This was undertaken using the transition probabilities representing the natural

progression of chronic HCV infection estimated by Shepherd et al. in their table 37, over a 20-year period.

Antiviral treatment for chronic HCV infection was assumed to be pegylated interferon alpha plus ribavirin, initiated at the onset of chronic disease, for a period of 37.8 weeks [62]. No further HCV specific drug treatments were assumed after this point.

The health care and other wider costs associated with successful and unsuccessful OST treatment were taken from Goddard et al [63]. (and again repeated in a recent HTA report by Adi et al. [64]). This information was derived from the National Treatment Outcome Research Study (NTORS; [63]), which to date is the largest published prospective longitudinal cohort study of treatment outcome for IDUs in the UK. This model uses a similar approach to that taken by Adi et al. in so much that it is assumed that drug users not on OST are associated with annual mean costs that are equivalent to those reported by NTORS participants in the year prior to entering treatment. On the other hand, the annual mean costs reported by NTORS participants starting treatment within the following year (ie. those on treatment), were taken to represent the costs of successful treatment. Thus, the model assumes that people on OST are being 'successfully' treated, whereas those not on treatment, continue to be 'active' IDUs. Note that as the health care costs derived by the NTORS study are likely to include the costs of HIV and HCV infection, this model is likely to overestimate the costs associated with viral infections. The costs could not be unpicked any further

as the NTORS data are presented at a level that would not allow costs to be attributed to specific health problems, only treatment groupings

Table 4: Health state specific and other costs*

Resource item	Value	Source
Intervention		
One off total intervention cost for a 2 hour consultation	2 x £30**	Assumption based on data supplied by the NTA
Transport to initial consultation	£15	Assumption
HIV associated costs		
Symptomatic HIV infection	£11,677	Miners [60]
Asymptomatic HIV infection	£12,818	Miners [60]
AIDS	£25,563	Miners [60]
Cost of HAART	£3,201	Miners [60]
HCV associated costs		
HCV acute infection	£0	Assumption
HCV chronic infection	£629	Weighted average calculated from Shepherd 2007 [61]
HCV antiviral therapy$ (37.8$$ weeks treatment for mild HCV infection)	£8,269	Weight average calculated from Shepherd 2007 [61]
OST and IDU associated costs		
Health care costs of OST	£1,482	Dijkgraaf [59]
Health care costs of successful OST	£1,455	NTROS [63]
Health care costs of unsuccessful OST	£1,285	NTORS [63]
CJS and victim costs of successful OST	£18,327	NTORS [63] and Adi [64]
CJS and victim costs of unsuccessful OST	£40,136	NTORS [63] and Adi [64]

***costs are annual unless stated otherwise**
****national median value of a cost per contact with three tier providers (ie. excluding pharmacy exchange)**
$based on least costly drug combination (pegylated interferon alpha and ribavirin) and likely distribution of genotype (50% genotype 1 and 50% genotypes 2 and 3)
$$mean length of treatment from RCT of mild HCV treatment

2.11 Health-related Quality-of-life

The infectious disease model provided estimates of overall patient survival by simulating movements between various health states, including death. To transform these estimates into QALYs, information was required on the utility associated with each health state. A systematic literature search was undertaken to identify the necessary evidence. However, while a number of studies were identified, none reported particularly useful information. Therefore the following assumptions were made. First, IDUs with HCV infection were assumed to have utility values as reported and used by Shepherd et al in a non-IDU population (Table 5). However, as this report subdivided the health state chronic HCV infection into various chronic stages, a weighted average was calculated for the single chronic HCV health state in this model – 0.66 – in a manner identical to that used to calculate the weighted cost for this health state. Second, initial runs of the infectious disease component of the model suggested that nearly all patients with HIV were co-infected with HCV. As no useful evidence could be identified on the disutility associated with co-infection, an assumption was made that all HIV patients were indeed co-infected with HCV, and that they had utility values of 0.5, irrespective of stage of HIV. Lastly the utility values for all health states that included IDUs not on OST, were multiplied by a factor of 0.9, to represent the fact that IDUs are more likely to have lower HRQoL levels compared with non-IDU populations. The value of 0.9 is not evidence based, but is in line with values used in other similar modelling studies [65].

Table 5: Health state utilities

Health state	Value	Source
IDU no viral infection*	0.85	Assumption
asymptomatic HIV* and HCV	0.5	Assumption
symptomatic HIV* and HCV	0.5	Assumption
AIDS* and HCV*	0.5	Assumption
HCV acute infection*	0.7	Shepherd 2007 [61]
HCV chronic infection*	0.66	Weighted average calculated from Shepherd 2007 [61]
No viral infection and successful OST[$]	0.95	Assumption, based on Stein 2004 [66]

***values for these health states were multiplied by 0.9 for IDUs**
[$]No allowance is made for the length of time on successful OST

Standard economic practice is to rank alternative strategies in terms of increasing effectiveness, and to compare the costs and effects of neighbouring treatment pairs after removing strategies that are dominated or extendedly dominated. However, most of the analyses contained within this report were considered to be more representative of 'what if' or 'threshold' analyses, rather than strict comparisons of competing alternatives. Thus, unless otherwise stated, ICERs were calculated with reference to the relevant baseline analysis.

3 Results

3.1 Base case results of the economic analysis

The main results are reported in Table 6 and 7 using a societal perspective. In all scenarios, the intervention to increase participation to OSTs (from 13.5% to 107.8%) was shown to be the dominant option compared with the baseline. However, the results also showed that ever increasing recruitment rates to OST led to ever increasing estimates of cost-effectiveness. For example, assuming an increase in recruitment to OSTs in Bristol of 107.8%, was associated with a total cost of 432,846,008 and 10,861 QALYs. This cost was lower than for any of the other OST-related scenarios including the baseline, and was also the scenario associated with the highest number of QALYs. The same was also true in the lower HCV prevalence setting (i.e. Teesside).

The threshold analysis for interventions to increase recruitment to high syringe coverage (defined as those IDUs with greater than 100% syringe coverage, i.e. obtain more syringes than they inject per week) groups / reduce the rate at which IDUs left high coverage groups produced a mixed set of results. For example, Table shows that at a threshold willingness to pay of £20,000 per additional QALY, no additional cost would be acceptable if an intervention to increase recruitment rates to the high syringe coverage group increased the recruitment rate by12.5% in Teesside, as the ICER for this scenario was £29,309. However, at a threshold willingness pay of £30,000, scope existed for a positive additional intervention cost, although the value was only £1 per IDU. Understandably, increasing effectiveness was

associated with increasing additional cost thresholds. So, for example, for Teesside at a threshold willingness to pay of £30,000 per additional QALY, an additional intervention cost of up to £341 per IDU would be acceptable if the recruitment rates to the high syringe coverage group increased by 100%.

The cost thresholds for increasing recruitment to HCV treatment showed that the scope for interventions to be cost-effective was reasonably high. For example table 5 shows that at a willingness to pay of £20,000 per additional QALY, an additional £1,078 per IDU would be acceptable in Bristol if an intervention increased recruitment from approximately 0% (see baseline assumptions in Table 2) to 5% per year. This increases to £4,429 in Bristol for a willingness to pay of £30,000 per additional QALY.

Note that cost thresholds in the lower prevalence setting of Teesside tended to be higher compared with Bristol (suggesting that larger increases in cost are acceptable), and ICERs lower compared with higher HCV prevalence settings. This is primarily because IDUs in higher HCV prevalence settings are more likely to be reinfected further down the line, thus the effectiveness of interventions to reduce the incidence of infections appears reduced.

3.2 Sensitivity analysis on cost and utility data

Sensitivity analysis showed that restricting the cost perspective to that of the NHS / PSS (see Table 8 and 9) altered the expected costs and QALYs. Note that restricting the cost perspective (that is, not including the costs of IDU-

associated crime) increased the cost-effectiveness of interventions to increase recruitment to high syringe coverage groups / reduce the rate at which IDUs leave high coverage syringe groups. This is because increasing the expected survival via interventions to reduce syringe sharing increases the life-expectancy of IDUs, and therefore also increases the expected value of IDU-associated crime. Thus, restricting the costs to those of the NHS / PSS alone, reduced the overall costs associated with increasing the life expectancy of IDUs. However, in the scenarios to increase recruitment rates to OST, restricting the cost perspective reduced cost-effectiveness, as the cost savings of reducing IDU-associated crime were no longer considered.

Further basic one-way sensitivity analysis for the OST scenario showed that the ICERs were not sensitive to most of the cost and utility variables including changes in the cost of HIV care, HAART, the cost of chronic HCV infection, the costs of the intervention, the cost of OST treatment (eg. administering methadone), the utility associated to HCV infection or the IDU weighting factor. Indeed, despite significant changes to these and other variables, the intervention remained 'dominant' in most scenarios (that is, less costly and more effective compared with the baseline [see Table 10]).

Table 6: Base case results (Bristol) – societal perspective (all scenarios are compared with the baseline, as they effectively represent sensitivity analysis unless otherwise stated)

Scenario	% increase in OST recruit rate	% increase in 100% coverage recruitment rate	% decrease in 100% coverage leaving rate	Costs (£)	QALYs	ICER	£20,000 Threshold[$]	£30,000 Threshold[$]
Baseline				481,129,096	10,563	-		
Interventions to increase recruitment to high syringe coverage*								
	0%	12.5%	0%	481,248,303	10,566	£38,679	Not c/e	Not c/e
	0%	25%	0%	481,251,065	10,569	£19,864	£1	£62
	0%	50%	0%	481,243,248	10,574	£9,848	£118	£234
	0%	100%	0%	481,318,473	10,583	£4,359	£321	£526
Intervention to reduce rate IDUs leave high coverage group*								
	0%	0%	12.5%	481,245,327	10,565	£45,821	Not c/e	Not c/e
	0%	0%	25%	481,251,602	10,568	£22,078	Not c/e	£44
	0%	0%	50%	481,260,208	10,576	£9,890	£134	£267
	0%	0%	75%	481,224,069	10,586	£4,088	£370	£602
Intervention to increase recruitment on OST								

	13.5%	0%	0%	473,111,950	10,612	Dominant		
	26.9%	0%	0%	465,789,808	10,657	Dominant		
	53.8%	***0%***	***0%***	***452,949,611***	***10,737***	***Dominant***		
	107.8%	0%	0%	432,846,008	10,861	Dominant		
Intervention to increase recruitment to HCV antiretroviral treatment*								
Base case	0%	0%	0%	£481,161,632	10,266			
5%	0%	0%	0%	£482,353,143	10,380	£10,500	£1,078	£2,213
10%	0%	0%	0%	£483,396,578	10,488	£10,062	£2,208	£4,429

***assumes zero cost of intervention to increase recruitment rate or to decrease recruitment loss**

[$]Results shown represent an average per person increase in costs to achieve the stated threshold

Bold italics = base case scenario

Table 7: Base case results (Teesside) – societal perspective (all scenarios are compared with the baseline, as they effectively represent sensitivity analysis unless otherwise stated)

Scenario	% increase in OST recruit rate	% increase in 100% coverage recruitment rate	% decrease in 100% coverage leaving rate	Costs (£)	QALYs	ICER	£20,000 Threshold[$]	£30,000 Threshold[$]
Baseline				£375,057,269	10,998	-		
Interventions to increase recruitment to high syringe coverage*								
	0%	12.5%	0%	£375,114,253	11,000	£29,309	not c/e	£1
	0%	25%	0%	£375,101,736	11,002	£12,285	£28	£64
	0%	50%	0%	£375,081,316	11,005	£3,669	£107	£173
	0%	100%	0%	£375,074,979	11,010	£1,483	£221	£341
Intervention to reduce rate IDUs leave high coverage group*								
	0%	0%	12.5%	£375,106,936	11,000	£31,106	not c/e	not c/e
	0%	0%	25%	£375,099,311	11,002	£12,564	£25	£58
	0%	0%	50%	£375,090,317	11,006	£4,037	£131	£213
	0%	0%	75%	£375,049,718	11,013	Dominant	£295	£438
Intervention to increase recruitment on OST								

	13.5%	0%	0%	£368,578,145	11,038	Dominant		
	26.9%	0%	0%	£363,086,338	11,072	Dominant		
	53.8%	***0%***	***0%***	***£354,258,709***	***11,126***	***Dominant***		
	107.8%	0%	0%	£342,234,596	11,201	Dominant		
Intervention to increase recruitment to HCV antiretroviral treatment*								
Base case				£374,820,539	10,898			
5%	0%	0%	0%	£375,454,450	10,958	£10,623	£560	£1,156
10%	0%	0%	0%	£375,300,508	11,012	£4,232	£1,788	£2,923

***assumes zero cost of intervention**

[$]Results shown represent an average per person increase in costs to achieve the stated threshold

Bold italics = base case scenario

Table 8: ICERs for Bristol using a health services perspective (all scenarios are compared with the baseline, as they effectively represent sensitivity analysis unless otherwise stated)

Scenario	% increase in OST recruit rate	% increase in 100% coverage recruitment rate	% decrease in 100% coverage leaving rate	Costs (£)	QALYs	ICER	£20,000 Threshold[$]	£30,000 Threshold[$]
Baseline				£35,280,909	10,563	-		
Interventions to increase recruitment to high syringe coverage*								
	0%	12.5%	0%	£35,378,211	10,566	£31,572	not c/e	not c/e
	0%	25%	0%	£35,351,080	10,569	£11,428	£53	£114
	0%	50%	0%	£35,302,286	10,574	£1,844	£210	£326
	0%	100%	0%	£35,220,125	10,583	Dominant	£471	£676
Intervention to reduce rate IDUs leave high coverage group*								
	0%	0%	12.5%	£35,383,049	10,565	£40,266	not c/e	not c/e
	0%	0%	25%	£35,355,424	10,568	£13,429	£36	£92
	0%	0%	50%	£35,287,261	10,576	£479	£259	£391
	0%	0%	75%	£35,193,478	10,586	Dominant	£552	£784
Intervention to increase recruitment on OST								

	13.5%	0%	0%	£36,103,502	10,612	£16,568		
	26.9%	0%	0%	£36,730,131	10,657	£15,315		
	53.8%	0%	0%	£37,830,602	10,737	£14,651		
	107.8%	0%	0%	£39,550,586	10,861	£14,297		
Intervention to increase recruitment to HCV antiretroviral treatment*								
Base case				£34,514,033	10,266			
5%	0%	0%	0%	£35,948,737	10,380	£12,644	£835	£1,969
10%	0%	0%	0%	£37,273,985	10,488	£12,425	£1,683	£3,904

***assumes zero cost of intervention to increase recruitment rate or to decrease recruitment loss**

[$]Results shown represent an average per person increase in costs to achieve the stated threshold

Table 9: ICERs for Teesside using a health services perspective (all scenarios are compared with the baseline, as they effectively represent sensitivity analysis unless otherwise stated)

Scenario	% increase in OST recruit rate	% increase in 100% coverage recruitment rate	% decrease in 100% coverage leaving rate	Costs (£)	QALYs	ICER	£20,000 Threshold[$]	£30,000 Threshold[$]
Baseline				£36,031,798	10,998			
Interventions to increase recruitment to high syringe coverage*								
	0%	12.5%	0%	£36,082,637	11,000	£26,148	not c/e	£7
	0%	25%	0%	£36,074,531	11,002	£11,806	£30	£66
	0%	50%	0%	£36,059,671	11,005	£4,253	£103	£169
	0%	100%	0%	£36,036,775	11,010	£417	£234	£353
Intervention to reduce rate IDUs leave high coverage group*								
	0%	0%	12.5%	£36,083,805	11,000	£32,571	not c/e	not c/e
	0%	0%	25%	£36,075,436	11,002	£13,041	£23	£57
	0%	0%	50%	£36,055,785	11,006	£2,931	£140	£222
	0%	0%	75%	£36,025,120	11,013	Dominant	£294	£437

Intervention to increase recruitment on OST								
	13.5%	0%	0%	£36,653,756	11,038	£15,597		
	26.9%	0%	0%	£37,125,486	11,072	£14,045		
	53.8%	0%	0%	£37,881,690	11,126	£14,038		
	107.8%	0%	0%	£38,914,997	11,201	£13,793		
Intervention to increase recruitment to HCV antiretroviral treatment*								
Base case				£35,798,397	10,898			
5%	0%	0%	0%	£36,430,874	10,958	£10,599	£561	£1,158
10%	0%	0%	0%	£36,272,630	11,012	£4,181	£1,794	£2,928

***assumes zero cost of intervention to increase recruitment rate or to decrease recruitment loss**

[$]**Results shown represent an average per person increase in costs to achieve the stated threshold**

Table 10: One way sensitivity analysis on utility and cost variables for the base case scenario to increase participation rates to OST (using a societal perspective)

Parameter	Original Value	New Value	ICER	
			Bristol*	Teesside*
HAART	£3,201	£0	Dominant	Dominant
HCV antiviral therapy	£8,269	£0	Dominant	Dominant
Cost for chronic HCV	£29	£0	Dominant	Dominant
IDU disutility factor	0.9	1	Dominant	Dominant
HIV-related health states	0.5[+]	0	Dominant	Dominant
Successful OST	0.95	0.9	Dominant	Dominant
Utility for acute HCV infections	0.77	0.7	Dominant	Dominant
Utility for chronic HCV infection	0.66	0.6	Dominant	Dominant
Intervention cost per IDU	£75	£150	Dominant	Dominant
NHS / PSS cost perspective	-	-	£14,651	£14,038

***Indicates that in the base case the intervention to increase participation to OST was 'dominant'**

[+]As all IDUs with HIV infection were also assumed to have HCV infection, this value is equivalent to considering co-infection

3.3 Impact projections on HCV transmission

In addition to determining whether an intervention is a worth while use of resources, it is also important to understand whether it will result in a noticeable reduction in the incidence of prevalence of HIV/HCV. Because the prevalence of HIV is very low, and generally easier to control than HCV, this impact analysis mainly focuses on the transmission of HCV. However, to summarise, there was negligible HIV in Teesside and for Bristol the impact of all the interventions, except HCV treatment, resulted in a two to three fold larger relative decrease in HIV prevalence over 20 years than was projected for HCV (Table 13).

As found in two recent studies ([53] and unpublished data from South Wales [67], see Tables 11 and 12), our model projected there is a much lower incidence of HCV amongst IDUs that are currently on OST and/or have over 100% syringe coverage (Figure 4). However, despite this, most of the non-HCV treatment interventions modelled in this analysis result in a relatively small decrease in the HCV incidence in either setting (Table 13), normally <10% in Teesside and <5% in Bristol over 20 years. This is because IDUs still have periods of high risk sharing (possibly due to homelessness or imprisonment) when they are not on OST or do not have >100% syringe coverage, and many still share even when on OST and/or have >100% syringe coverage (obtain more syringes than they need). Only multifaceted interventions that include both increases in OST recruitment and the rate at which IDUs achieve >100% syringe coverage result in more than 20% decrease in HCV incidence and 10% decrease in HCV prevalence over 20

years. To attain greater impact than this, IDUs need to further reduce their frequency of sharing syringes or injecting equipment whilst on OST or >100% syringe coverage (results not shown), or the coverage of HCV treatment needs to be increased (see below or Table 13 for details). Also, it is important to bear in mind that cross sectional studies which sample active IDU are likely to under-estimate intervention effect of OST as shown by prospective studies (such as Amsterdam Cohort Study and Wales incidence study) – as the former studies exclude IDU that have ceased injecting for a period during OST which are included in the latter studies.

Interestingly, our projections suggest that HCV treatment at low recruitment rates (5-10% per year) is likely to be an effective method of HCV prevention, resulting in up to a 20% decrease in incidence if 10% of chronic HCV IDUs are treated each year. This is despite the model assuming that up to 50% of treated IDUs are at risk of re-infection [6-8, 10, 40]. In addition, the inclusion of HCV treatment can significantly increase the impact of interventions that are focusing on increasing the number of IDUs on OST and >100% syringe coverage, with our projections suggesting that it can roughly double the impact of the intervention resulting in a 30 to 40% decrease in HCV incidence and up to a 20% decrease in prevalence (Table 13).

Table 11: HCV incidence by level of harm reduction in Amsterdam longitudinal IDU cohort [53]

Harm Reduction	HCV incidence per 100 person years	IRR	95% CI
None	23.2	1	
Incomplete	24.1	1.04	0.53-2.05
Full	3.5	0.15	0.056-0.40

Table 12: HCV incidence by level of syringe coverage and whether currently on OST in South Wales IDU cohort [67]

Coverage	HCV incidence per 100 person years	IRR	95% CI
<100% syringe coverage and no OST	9.7%	1	
>100% syringe coverage and no OST	11.1%	1.14	0.3-4.2
<100% syringe coverage and OST	5.7%	0.58	0.1-2.9
>100% syringe coverage and OST	1.6%	0.17	0.02-1.0

Table 13: Impact of different interventions on HCV incidence and HIV/HCV prevalence after 20 years

Intervention scenario	% decrease in HCV incidence		% decrease in HCV prevalence		% decrease in HIV prevalence
	Teesside	Bristol	Teesside	Bristol	Bristol
Increase in OST recruitment rate					
13.5%	1.9%	1.2%	1.1%	0.3%	2.4%
27%	3.6%	2.3%	2.1%	0.6%	4.5%
54%	6.3%	4.3%	3.7%	1.2%	7.7%
108%	10.1%	7.5%	6.0%	2.2%	12.2%
Increase in recruitment rate on to >100% syringe coverage					
12.5%	0.9%	0.7%	0.6%	0.2%	1.7%
25%	1.8%	1.4%	1.1%	0.5%	3.2%
50%	3.3%	2.7%	2.0%	0.9%	5.7%
100%	5.8%	4.9%	3.6%	1.6%	9.5%
Decrease in recruitment rate on to >100% syringe coverage					
12.5%	0.8%	0.6%	0.5%	0.2%	1.5%
25%	1.6%	1.2%	1.0%	0.4%	3.1%
50%	3.9%	3.0%	2.5%	1.0%	6.9%
75%	7.3%	5.7%	4.7%	1.9%	11.7%
Recruitment of IDUs on to HCV treatment					
5% per year	10.2%	7.6%	6.4%	3.0%	0%
10% per year	20.4%	16.4%	13.0%	6.4%	0%
100% increase in OST recruitment rate and 75% decrease in leaving OST					
	16.1%	16.2%	9.8%	5.0%	21.0%
100% increase in recruitment to >100% coverage and 75% decrease in leaving >100% coverage					
	12.8%	11.4%	8.2%	4.0%	18.0%
Combination of two previous interventions					
	22.6%	22.7%	14.3%	7.8%	25.2%
Previous intervention and 10% recruitment rate on to HCV treatment					
	42.1%	39.0%	27.7%	15.6%	25.2%
54% increase in OST recruitment rate, 50% decrease in leaving OST, 50% increase in recruitment to >100% coverage, 50% decrease in leaving >100% coverage, and 10% recruitment rate on to HCV treatment					
	35.7%	30.6%	23.1%	11.8%	19.6%

Figure 4a: Model projected HCV incidence by level of syringe coverage and whether currently on OST in Teesside and Bristol

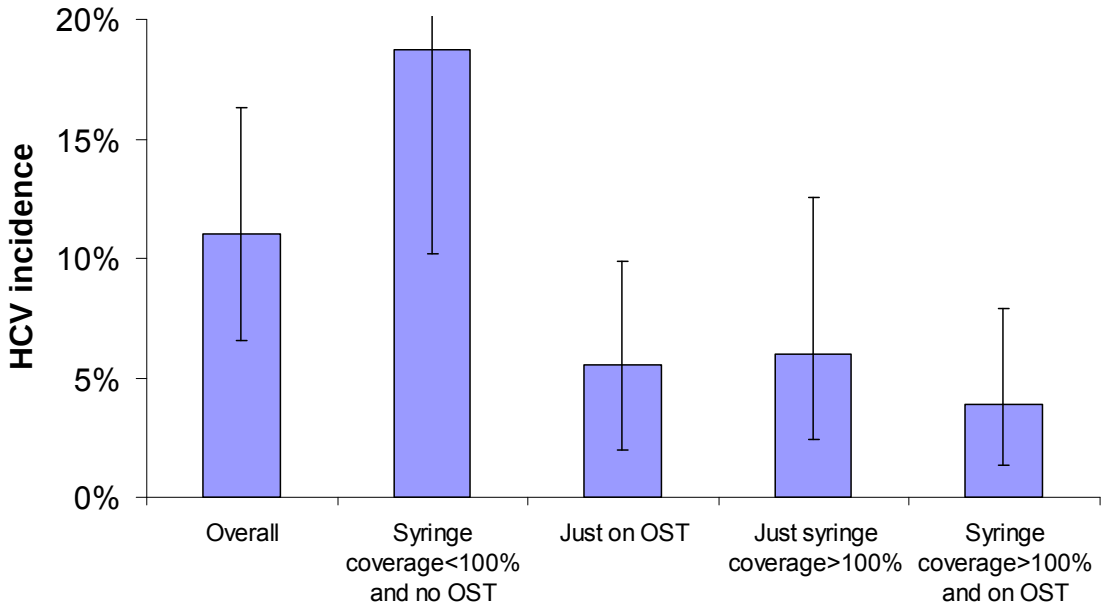
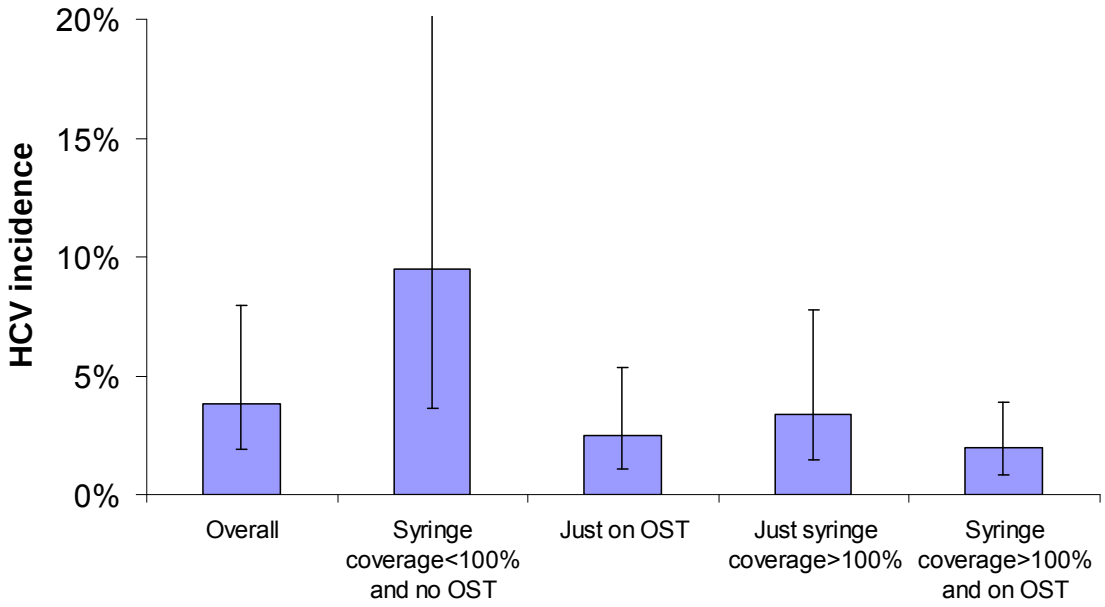


Figure 4b: Teesside



4 Discussion

The aim of this evaluation was to assess the cost-effectiveness of NSP-related activities, and their likely impact on HCV / HIV transmission. The first step in this process was to identify these interventions / services given the wide array of possibilities described in the scope document. They were determined by way of access to pre-existing infectious diseases models, and the availability of published evidence on the effectiveness of possible interventions.

The systematic review of the clinical literature identified a number of existing reviews and 22 primary studies evaluating a range of NSP-related activities. However, they were generally of very limited usefulness in terms of identifying interventions on which to base an economic evaluation and providing useful information on the effectiveness outcomes. The only study of any substantive use from the effectiveness review was a RCT by Strathdee et al, in which a 'strengths-based management-model' to increase participation rates in OST programmes was evaluated. The RCT suggested there to be some benefit of the intervention, compared with no 'active encouragement', in terms of attendance at an initial treatment meeting. In addition, two other interventions were evaluated. One was based on an unpublished study by Wilkinson et al. [43], that evaluated an intervention to increase the recruitment of IDUs on to HCV treatment through an NSP based specialist clinic, and the second explored the relationship between syringe coverage (defined as the number of syringes they obtain divided by the number of injections an IDU has per unit time) and syringe sharing. Although a specific intervention was not described

in this study, it was evaluated to address question 1 - to explore the likely impact of any intervention that would increase the coverage of syringes to IDUs. Possible interventions could include opening the NSPs longer, or using a mobile van or vending machines to increase distribution out of normal opening hours.

An infectious disease model, simulating movements between active and non-active injecting IDU health states and stages of HCV / HIV-related infection, was assembled to evaluate the cost-effectiveness of the interventions, in two contrasting HCV epidemiological settings.

At face value, the result from the economic analysis contained herein suggests that the intervention to increase OST participation rates is likely to be cost-effective as are interventions to increase the uptake of HCV treatments or the coverage of syringe distribution (if moderately effective and of modest cost). However, there are a number of limitations with the evaluation. Although the analysis used a dynamic HIV and HCV transmission model to estimate the impact of the interventions, and used detailed site specific data to parameterise the model, the inherent uncertainty in many behavioural and biological parameters led to difficulties in fitting the model. To counter this, a fitting procedure was used to produce multiple model fits to the data, and so the model impact projections incorporated the parameter uncertainties. While the analysis did explore whether the modelled interventions would impact on HIV/HCV transmission amongst IDUs, it did not specifically determine the required coverage of these interventions to attain

specific reductions in HIV/HCV prevalence or incidence.

The analysis was also limited in a number of other ways, mainly relating to uncertainties in the data needed to parameterise the model. Specifically, there was uncertainty around many of the biological parameters, including the proportion of new HCV infecteds that resolve their infection, the relative difference between the HIV and HCV transmission probabilities per syringe sharing act, the degree to which HIV and HCV can be transmitted through sharing other injecting equipment, and the nature of HCV immunity after resolution of infection and treatment. There are also thought to be biases in some of the IDU behavioural data such as the proportion of IDUs that report syringe sharing and the frequency with which they share. Lastly, there are uncertainties in the coverage of existing interventions for IDUs, such as the percentage of eligible IDUs that are on HAART or HCV treatment. Following a review of the literature, analyses of available data sources, and communications with known experts, all the parameters were assigned ranges or 'likely' point estimates and many of the uncertainties were incorporated in the model fitting. Another weakness of the modelling was the lack of site specific longitudinal HIV and HCV data to fit the model to. However, country wide data suggests that the prevalences of both infections are fairly stable [16] and so the model fitting assumed they were roughly endemic, or in a slow state of flux.

The cost-effectiveness estimates of increasing participation rates to OST were substantially driven by cost offsets of reducing IDU-associated crime. These

costs were included by making an assumption within the model that IDUs not on OST were responsible for annual mean costs that were equivalent to those reported by NTORS participants in the year prior to entering treatment. On the other hand, the annual mean costs reported by NTORS participants starting treatment within the following year (i.e. those on treatment), were taken to represent the costs of successful treatment. Although this approach was viewed as the most appropriate given the availability of the evidence, it does have the potential to overestimate the cost-effectiveness of the intervention given that it implicitly assumes that IDUs on OST are at least partially adhering to their treatment. Moreover, the sensitivity analysis showed that the results were sensitive to the broadening of the perspective, if not the decision on cost-effectiveness.

The primary outcome measured in the Strathdee RCT was the proportion of IDUs attending an initial OST meeting within seven days of referral from the NSP. An assumption was made within the model that this outcome translated into increased numbers of IDUs attending OST, and that this ultimately resulted in fewer secondary HCV and HIV infections. While evidence exists for the latter relationship, evidence linking case management with improvements in health behaviour is thought to be inconclusive [68]. Thus, if such a relationship is not believed to exist, the value of increasing participation rates to an initial OST meeting is minimal, and has been overestimated herein.

Technical limitations of the model aside, there was an issue regarding the appropriate decision problems that have been evaluated in this report. That is, availability and access to existing NSP-related decision models and published evidence on the effectiveness of interventions / treatment strategies dictated the decision problems, rather conversations about specific aspects of NSP services that warranted particular attention. This approach was taken purely for pragmatic reasons, but it is acknowledged that no attempt has been made to evaluate other potentially important aspects of NSP provision, such as prison NSPs or interventions to reduce bacterial infections or overdose deaths (although assumptions about this have been made in relation to OST), for which clinical data were thought to be unavailable or it was thought to be beyond the scope of the model.

Lastly, the model analysis did not consider the possibility that needle exchanges could lead to an increase in both new injectors and in the duration of an existing IDU's injecting life due to it making injecting safer, and being viewed as condoning injection drug use. Although no data exist on these effects, it is possible that they could dilute the benefits of needle exchanges and may even reverse them if the effects are large enough.

4.1 Cost-effectiveness evidence summary

1. What level of coverage of needle and syringe programmes (NSPs) is the most effective and cost-effective

Results from the threshold modelling for decision problem 2 suggest that effective interventions to increase syringe coverage could be cost effective if the associated intervention costs are modest, given a societal cost perspective. Moreover, interventions in relatively low prevalence areas of HCV infection (such as Teesside) are likely to be more cost-effective than interventions in relatively high HCV prevalence areas, as it is 'easier' to control epidemics in the former. In contrast, interventions to increase syringe coverage in areas with a higher prevalence of HCV are less likely to be cost-effective. However, for both settings, the modelling results also suggest that although increasing the coverage of syringe distribution or the recruitment rate onto OST is sufficient for controlling HIV, it is insufficient for reducing the prevalence/incidence of HCV. As also found in recent studies from Amsterdam and Wales (Tables 9 and 10), our results suggest that multi-faceted interventions are needed to achieve substantial decreases in HCV incidence. These multi-faceted interventions need to increase the recruitment rate on to OST and attaining high syringe coverage, and could include HCV antiviral treatment to attain even greater decreases in HCV incidence.

2. **What types of NSP are effective and cost-effective?**

The quality and availability of the evidence did not permit any cost-effectiveness modelling for this question to be undertaken.

3. **Which additional harm-reduction services offered by NSPs are effective and cost effective?**

Results from the economic modelling for decision problem 1 suggest that interventions to encourage NSPs users to attend OST programmes are likely to be cost-effective even if the increase in participation rates is only modest. The impact on blood borne viruses may only be modest though unless it is undertaken as part of a group of interventions to reduce their transmission. However, the quality of the evidence demonstrating a positive effect of interventions to increase participation rates is poor.

The results for the evaluation of decision problem 3 also suggested that interventions to increase IDUs access to HCV antiviral therapies are likely to be cost-effective if they can be delivered at modest cost. They are also likely to be effective for reducing the transmission of HCV if sufficient HCV infected IDUs are recruited on to treatment each year (10% or more).

4. Are NSPs delivered in parallel with, or alongside, opiate substitution therapy (OST) effective and cost-effective?

The quality and availability of the evidence did not permit any cost-effectiveness modelling for this topic to be undertaken. However, the related decision problem of increasing the recruitment rate on to OST of IDUs attending NSPs was explored, and was found to be cost-effective.

References:

1. Millson P, Challacombe L, Villeneuve PJ, Strike CJ, Fischer B, Myers T*, et al.* **Reduction in injection-related HIV risk after 6 months in a low-threshold methadone treatment programme** *AIDS education and prevention* 2007,19:124-136.
2. Riley ED, Safaeian M, Strathdee SA, Marx MA, Huettner S, Beilenson P, Vlahov D. **Comparing New Participants of a Mobile Versus a Pharmacy-Based Needle Exchange Program**. *JAIDS* 200,24:57-61.
3. Bluthenthal RN, Ridgeway G, Schell T, Anderson R, Flynn NM, Kral AH. **Examination of the association between syringe exchange program (SEP) dispensation policy and SEP client-level syringe coverage among injection drug users**. *Addiction* 2007,102:638-646.
4. Strathdee SA, Ricketts EP, Huettner S, Cornelius L, Bishai D, Havens JR*, et al.* **Facilitating entry into drug treatment among injection drug users referred from a needle exchange program: Results from a community-based behavioral intervention trial**. *Drug Alcohol Depend* 2006,83:225-232.
5. Vickerman P, Hickman M, Judd A. **Modelling the impact of hepatitis C transmission of reducing syringe sharing: London case study.** *International Journal of Epidemiology* 2007,36:396-405.
6. Micallef JM, Macdonald V, Jauncey M, Amin J, Rawlinson WD, Van Beek I*, et al.* **High incidence of hepatitis C virus reinfection within a cohort of injecting drug users**. *Journal of Viral Hepatitis* 2007,14:413-418.
7. Currie SL, Ryan JC, Tracy D, Wright TL, George S, McQuaid R*, et al.* **A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus**. *Drug Alcohol Depend* 2008,93:148-154.
8. Grebely J, Conway B, Raffa JD, Lai C, Krajden M, Tyndall MW. **Hepatitis C virus reinfection in injection drug users**. *Hepatology* 2006,44:1139-1145.
9. Aitken CK, Tracy SL, Revill P, Bharadwaj M, Bowden DS, Winter RJ, Hellard ME. **Consecutive infections and clearances of different hepatitis C virus genotypes in an injecting drug user**. *J Clin Virol* 2008,41:293-296.
10. Dalgard O. **Follow-up studies of treatment for hepatitis C virus infection among injection drug users**. *Clin Infect Dis* 2005,40 Suppl 5:S336-338.
11. Hickman M, Carnwath Z, Madden P, Farrell M, Rooney R, Ashcroft R*, et al.* **Mortality and fatal overdose risk - pilot cohort study of heroin users recruited from specialist drug treatment sites in London**. *Journal of Urban Health* 2003,90:274-287.
12. Brettle RP, Chiswick A, Bell J, Busuttil A, Wilson A, Povey S, Leen CL. **Pre-AIDS deaths in HIV infection related to intravenous drug use**. *Qjm* 1997,90:617-629.
13. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, Garcia de Olalla P, de la Fuente L. **Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain**. *Addiction* 2005,100:981-989.

14. Davoli M, Bargagli AM, Perucci CA, Schifano P, Belleudi V, Hickman M*, et al.* **Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study**. *Addiction* 2007,102:1954-1959.
15. Hickman M, McDonald T, Judd A, Nichols T, Hope V, Skidmore S, Parry J. **Increasing the uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment and prison settings by using dried blood spots for diagnostic testing: a cluster randomised trial**. *Journal of Viral Hepatitis* 2008,15:250-254.
16. Health Protection Agency. **Shooting up. Infections among injecting drug users in the United Kingdom 2006**. In. London; 2007.
17. Baggaley RF, Boily MC, White RG, Alary M. **Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis**. *AIDS* 2006,20:805-812.
18. Kaplan EH, Heimer R. **A model-based estimate of HIV infectivity via needle sharing**. *Journal of Acquired Immune Deficiency Syndrome* 1992,5:1116-1118.
19. Hudgens MG, Longini IM, Jr., Vanichseni S, Hu DH, Kitayaporn D, Mock PA*, et al.* **Subtype-specific transmission probabilities for Human Immunodeficiency Virus among injecting drug users in Bangkok, Thailand**. *American Journal of Epidemiology* 2002,155:159-168.
20. Foss AM, Watts CH, Vickerman P, Azim T, Guinness L, Ahmed M*, et al.* **Could the CARE-SHAKTI intervention for injecting drug users be maintaining the low HIV prevalence in Dhaka, Bangladesh?** *Addiction* 2007,102:114-125.
21. Pilcher CD, Price MA, Hoffman IF, Galvin S, Martinson FE, Kazembe PN*, et al.* **Frequent detection of acute primary HIV infection in men in Malawi**. *AIDS* 2004,18:517-524.
22. Pilcher CD, Tien H, Vernazza PL, Stewart P, Chakraborty H, Eron JJ, Jr., Cohen MS. **Semen viral dynamics in acute HIV infection: implications for sexual transmission [Abstract ThOrC1489]**. *14th International AIDS Conference*. Barcelona, Spain 2002.
23. Pilcher CD, Tien HC, Eron JJ, Jr., Vernazza PL, Leu SY, Stewart PW*, et al.* **Brief but efficient: acute HIV infection and the sexual transmission of HIV**. *J Infect Dis* 2004,189:1785-1792.
24. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O*, et al.* **Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda**. *J Infect Dis* 2005,191:1403-1409.
25. Brettle RP, McNeil AJ, Burns S, Gore SM, Bird AG, Yap PL*, et al.* **Progression of HIV: follow-up of Edinburgh injecting drug users with narrow seroconversion intervals in 1983-1985**. *AIDS* 1996,10:419-430.
26. Prins M, Brettle RP, Robertson JR, Hernandez Aguado I, Broers B, Carre N*, et al.* **Geographical variation in disease progression in HIV-1 seroconverted injecting drug users in Europe?** *Int J Epidemiol* 1999,28:541-549.
27. van Asten L, Zangerle R, Hernandez Aguado I, Boufassa F, Broers B, Brettle RP*, et al.* **Do HIV disease progression and HAART response**

vary among injecting drug users in Europe? *Eur J Epidemiol* 2005,20:795-804.

28. Rodriguez-Arenas MA, Jarrin I, del Amo J, Iribarren JA, Moreno S, Viciana P*, et al.* **Delay in the initiation of HAART, poorer virological response, and higher mortality among HIV-infected injecting drug users in Spain**. *AIDS Res Hum Retroviruses* 2006,22:715-723.
29. Sterne JA, Hernan MA, Ledergerber B, Tilling K, Weber R, Sendi P*, et al.* **Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study**. *Lancet* 2005,366:378-384.
30. Health Protection Agency. **Survey of Prevalent HIV infections diagnosed (SOPHID - http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListDate/Page/1201094588844?p=1201094588844)**. In. London; 2007.
31. Baggaley RF, Garnett GP, Ferguson NM. **Modelling the impact of antiretroviral use in resource-poor settings**. *PLoS Med* 2006,3:493-504.
32. Cu-Uvin S, Caliendo AM, Reinert S, Chang A, Juliano-Remollino C, Flanigan TP*, et al.* **Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA**. *Aids* 2000,14:415-421.
33. Perelson AS, Essunger P, Cao Y, Vesanen M, Hurley A, Saksela K*, et al.* **Decay characteristics of HIV-1-infected compartments during combination therapy**. *Nature* 1997,387:188-191.
34. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire Mangen F*, et al.* **Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group**. *New England Journal of Medicine* 2000,342:921-929.
35. Fraser C, Hollingsworth TD, Chapman R, de Wolf F, Hanage WP. **Variation in HIV-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis**. *Proc Natl Acad Sci U S A* 2007,104:17441-17446.
36. Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H*, et al.* **Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa**. *AIDS Research and Human Retroviruses* 2001,17:901-910.
37. Cox AL, Netski DM, Mosbruger T, Sherman SG, Strathdee S, Ompad D*, et al.* **Prospective evaluation of community-acquired acute-phase hepatitis C virus infection**. *Clin Infect Dis* 2005,40:951-958.
38. Larghi A, Zuin M, Crosignani A, Ribero ML, Pipia C, Battezzati PM*, et al.* **Outcome of an outbreak of acute hepatitis C among healthy volunteers participating in pharmacokinetics studies**. *Hepatology* 2002,36:993-1000.
39. Micallef JM, Kaldor J, Dore GJ. **Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies**. *Journal of Viral Hepatitis* 2006,13:34-41.
40. Mehta SH, Cox A, Hoover DR, Wang XH, Mao Q, Ray S*, et al.* **Protection against persistence of hepatitis C**. *Lancet* 2002,359:1478-1483.

41. Irving WL, Smith S, Cater R, Pugh S, Neal KR, Coupland CA*, et al.* **Clinical pathways for patients with newly diagnosed hepatitis C - what actually happens**. *J Viral Hepat* 2006,13:264-271.
42. Jack K, Willott S, Manners J, Varnam M, Thomson BJ. **Aprimary care based model for the treatment of substance misusers infected with hepatitis C**. *Unpublished* 2008.
43. Wilkinson M, Crawford V, Tippet A, Jolly F, Turton J, Sims E*, et al.* **Community based treatment for chronic hepatitis C in drug users: High rates of compliance with therapy despiute on-going drug use**. *unpublished* 2008.
44. Grebely J, Genoway K, Khara M, Duncan F, Viljoen M, Elliott D*, et al.* **Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection**. *Int J Drug Policy* 2007,18:437-443.
45. Matthews G, Kronborg IJ, Dore GJ. **Treatment for hepatitis C virus infection among current injection drug users in Australia**. *Clin Infect Dis* 2005,40 Suppl 5:S325-329.
46. Jowett SL, Agarwal K, Smith BC, Craig W, Hewett M, Bassendine DR*, et al.* **Managing chronic hepatitis C acquired through intravenous drug use**. *Qjm* 2001,94:153-158.
47. Hickman M, Hope V, Brady T, Madden P, Jones S, Honor S*, et al.* **Hepatitis C virus (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004**. *J Viral Hepat* 2007,14:645-652.
48. Gibson DR, Flynn N, Perales D. **Effectiveness of syringe exchange programs in reducing HIV risk behavior and HIV seroconversion among injecting drug users**. *AIDS* 2001,15:1329-1341.
49. Hurley SF, Jolley DJ, Kaldor JM. **Effectiveness of needle-exchange programmes for prevention of HIV infection**. *Lancet* 1997,349:1797-1800.
50. Vickerman P, Kumaranayake L, Balakireva O, Guinness L, Artyukh O, Semikop TE*, et al.* **The cost-effectiveness of expanding harm reduction activities for injecting drug users in Odessa, Ukraine**. *Sexually Transmitted Diseases* 2006,33 supplement:S89-S102.
51. Kaplan EH, Heimer R. **A circulation theory of needle exchange [editorial]**. *AIDS* 1994,8:567-574.
52. Des Jarlais DC, Perlis T, Arasteh K, Torian LV, Hagan H, Beatrice S*, et al.* **Reductions in hepatitis C virus and HIV infections among injecting drug users in New York City, 1990-2001**. *AIDS* 2005,19 Suppl 3:S20-25.
53. van Den Berg C, Smit C, Van Brussel G, Coutinho RA, Prins M. **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* 2007,102:1454-1462.
54. Bluthenthal RN, Anderson R, Flynn NM, Kral AH. **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* 2007,89:214-222.

55. Heimer R, Clair S, Teng W, Grau LE, Khoshnood K, Singer M. **Effects of increasing syringe availability on syringe-exchange use and HIV risk: Connecticut, 1990-2001**. *Journal of Urban Health* 2002,79:556-570.
56. Kral AH, Anderson R, Flynn NM, Bluthenthal RN. **Injection risk behaviors among clients of syringe exchange programs with different syringe dispensation policies**. *J Acquir Immune Defic Syndr* 2004,37:1307-1312.
57. Vickerman P, Hickman M, Rhodes T, Watts CH. **Model projections on the required coverage of syringe distribution to prevent HIV epidemics among injecting drug users** *J Acquir Immune Defic Syndr* 2006,42:355-361.
58. Backmund M, Meyer K, Edlin BR. **Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users**. *Clin Infect Dis* 2004,39:1540-1543.
59. Dijkgraaf MGW, van der Zanden BP, de Borgie CAJM, Blanken P, van Ree JM, van den Brink W. **Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials**. *BMJ* 2005,330:1297-.
60. Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, Beck E. **Assessing the cost-effectiveness of HAART for adults with HIV in England**. *HIV Medicine* 2001,2:52-58.
61. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. **Interferon alfa (pegylated and non-pegylated) ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation**. *Health Technology Assessment* 2007,11.
62. Wright M, Forton D, Main J, Goldin R, Torok E, Tedder R. **Treatment of histologically mild hepatitis C virus infection with interferon and ribavirin: a multicentre randomised controlled trial**. *Journal of Viral Hepatitis* 2005,12:58-66.
63. Godfrey C, Stewart D, Gossop M. **Economic analysis of costs and consequences of the treatment of drug misuse: 2-year outcome data from the National Treatment Outcome Research Study (NTORS)**. *Addiction* 2004,99:697-707.
64. Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E*, et al.* **Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation** *Health Technology Assessment* 2007,11.
65. Barnett PG, Zaric GS, Brandeau ML. **The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States**. *Addiction* 2001,96:1267-1278.
66. Stein K, Dalziel K, Walker A, Jenkins B, Round A, Royle P. **Screening for Hepatitis C in injecting drug users: a cost utility analysis**. *Journal of Public Health* 2004,26:61-71.
67. Craine N, Hickman M, Parry J, Smith J, Walker A, Russel D*, et al.* **Hepatitis C Virus incidence amongst drug injectors: results from the South Wales prospective cohort study**. *Unpublished* 2008.
68. Hesse M, Vanderplasschen W, Rapp RC, Broekaert E, Fridell M. **Case management for persons with substance use disorders**. In: Cochrane Database of Systematic Reviews; 2007.

69. Kretzschmar M, Wiessing L. **Modelling the transmission of hepatitis C in injecting drug users**. In: *Hepatitis C and injecting drug use: impact, costs and policy options*. Edited by Jager JC, Limburg W, Kretzschmar M, Postma MJ, Wiessing L. Lisbon: European monitoring centre for drugs and drug addiction; 2004.
70. Lefrere JJ, Girot R, Lefrere F, Guillaume N, Lerable J, Le Marrec N*, et al.* **Complete or partial seroreversion in immunocompetent individuals after self-limited HCV infection: consequences for transfusion**. *Transfusion* 2004,44:343-348.
71. Lefrere JJ, Guiramand S, Lefrere F, Mariotti M, Aumont P, Lerable J*, et al.* **Full or partial seroreversion in patients infected by hepatitis C virus**. *J Infect Dis* 1997,175:316-322.
72. Takaki A, Wiese M, Maertens G, Depla E, Seifert U, Liebetrau A*, et al.* **Cellular immune responses persist and humoral responses decrease two decades after recovery from a single-source outbreak of hepatitis C**. *Nat Med* 2000,6:578-582.
73. Kondili LA, Chionne P, Costantino A, Villano U, Lo Noce C, Pannozzo F*, et al.* **Infection rate and spontaneous seroreversion of anti-hepatitis C virus during the natural course of hepatitis C virus infection in the general population**. *Gut* 2002,50:693-696.
74. Garnett GP, Anderson RM. **Balancing sexual partnerships in an age and activity stratified model of HIV transmission in heterosexual populations**. *IMA J Math Appl Med Biol* 1994,11:161-192.
75. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. **Methadone maintenance at different dosages for opiod dependence (Review)**. *The Cochrane Library* 2007.
76. Gossop M, Marsden J, Stewart D, Kidd T. **The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results**. *Addiction* 2003,98:291-303.

Appendix 1: Description of HCV and HIV model

HCV model description

Based on a brief review of HCV, a model was constructed to simulate the transmission of HCV in an IDU population. This Initial form of the model is an adaptation of a model developed by Kretzschmar and Wiessing [69]. Their model was modified to allow for two different types of acute infection – one leading to chronic infection and the other leading to self cure, and to allow more flexibility around the level of immunity/susceptibility present following resolution of infection. Figure 1 shows a flow diagram of the model.

The IDU population is divided in to those that are susceptible to HCV infection (*x if never been infected and x1 if been infected before*), those that are recently HCV infected and are in the initial acute phase of infection (*h1 and h2*), those who have progressed into the chronic phase (*y*), are on treatment (t), or have become immune (z1 and z2). In addition, each infection subgroup is also divided into two behavioural risk groups (denoted by a subscript i for whether they share with a low (i=0) or high frequency (i=1)), and two classes for the duration they have been injecting drugs (denoted by a subscript j for whether they have been injecting for a short (j=0) or long duration (j=1)) . Susceptibles are infected at a per capita rate π, dependent on the number of IDUs they share syringe with from each behavioural risk group, and the proportion that are in the acute or chronic phase of infection. All susceptibles that become infected progress to the acute phase of infection. However, a proportion δ are assumed to progress to the acute phase that leads to self curing, and the remainder '1-δ' progress to the acute phase that develops into chronic infection. The duration of the different acute phases is 1/σ. Chronic infecteds are assumed to remain infected until death. A proportion '1-α' of the self curers are assumed to become susceptible again, but with a positive antibody response, and the rest become immune, but may sero-revert after an average duration 1/η [70-73]. The chronic infecteds can be treated (at a rate φ), with the treatment lasting an average duration (1/ω) and having a probability ξ of curing their infection, and leading to immunity. The model is defined by the following differential equations:

$$\frac{dx_{ij}}{dt} = \Omega - x_{ij}\left(\pi_{ij} + \mu\right)$$
$$\frac{dx_{1ij}}{dt} = -x_{1ij}\left(\pi_{ij} + \mu\right) + \sigma\left(1-\alpha\right)h_{2,ij} + \omega\xi\left(1-\alpha\right)t_{ij}$$
$$\frac{dh_{1,ij}}{dt} = \pi_{ij}x_{ij}\left(1-\delta\right) - h_{1,ij}\left(\sigma + \mu\right)$$
$$\frac{dh_{2,ij}}{dt} = \pi_{ij}x_{ij}\delta - h_{2,ij}\left(\sigma + \mu\right)$$
$$\frac{dy_{ij}}{dt} = \sigma h_{1,ij} - \mu y_{ij} - \varphi y_{ij} + \omega\left(1-\xi\right)t_{ij}$$
$$\frac{dt_{ij}}{dt} = \varphi y_{ij} - \omega t_{ij}$$
$$\frac{dz_{1,ij}}{dt} = \sigma\alpha h_{2,ij} - z_{1,ij}\left(\mu + \eta\right) + \omega\xi\alpha t_{ij}$$
$$\frac{dz_{2,ij}}{dt} = \eta z_{1,i} - \mu z_{2,i}$$

Equation 1

The force of infection π_i is dependent on the number of IDUs in the acute and chronic phase of HCV infection, the probability of HCV transmission per syringe sharing incident for each phase of infection, the syringe sharing behaviour of the IDUs, and the degree to which IDUs mix with different syringe sharing risk groups:

$$\pi_{ij} = m_{ij}\sum_{\forall op}\frac{\rho_{ijop}}{N_{op}}\left[h_{1,op}B_{1,op}^{hcv} + h_{2,op}B_{2,op}^{hcv} + y_{op}B_{3,op}^{hcv}\right], \quad where \quad B_{e,op}^{hcv} = \left(1-\left(1-\beta_e^{hcv}\right)^{n_{op}}\right),$$

Equation 2

where m_{ij} is the number of syringe sharing partners they have per month for risk group i, n_{ij} is the number of times they receptively share a syringe with each of these partners, β_e^{hcv} is the HCV transmission probability per syringe sharing act for different stages of infection, N_{ij} is the size of the IDU syringe sharing risk and injecting duration group ij, and ρ_{ijop} is the probability that an IDU in syringe sharing risk and injecting duration group ij has a syringe sharing partner in syringe sharing risk and injecting duration group op, and has the following standard formulation:

$$\rho_{ijop} = (1-\varepsilon_{dur})(1-\varepsilon_{inj})\frac{m_{op}N_{op}}{\sum_{\forall r,s} m_{rs}N_{rs}} + (1-\varepsilon_{dur})\varepsilon_{inj}\delta_{io}\frac{m_{ip}N_{ip}}{\sum_{\forall s} m_{is}N_{is}} + (1-\varepsilon_{inj})\varepsilon_{dur}\delta_{jp}\frac{m_{oj}N_{oj}}{\sum_{\forall r} m_{rj}N_{rj}} + \varepsilon_{age}\varepsilon_{sex}\delta_{io}\delta_{jp},$$

Equation 3

Here δ_{jp} is the *dirac-delta* function that equals one if *j=p* and zero otherwise, and the parameters ϵ_{inj} and ϵ_{dur} determines the degree to which IDUs in a certain risk group and of a certain injecting duration form syringe sharing partnerships with IDUs of the same syringe sharing behaviour, or form them randomly depending on the number of syringe sharing partnerships provided by each syringe sharing and injecting duration group (1 is complete like with like assortative mixing and 0 is random mixing). The form and derivation of the ρ_{ijop} function is based on the formulation by Garnett and Anderson [74]. The product $m_{ij}\rho_{ijop}$ then gives the total number of syringe sharing partnerships an individual from sub-group *ij* forms with those from sub-group *op*.

HIV model description

A simple model was also combined in to the HCV model to simulate the transmission of HIV in the IDU population. The model assumes the same syringe sharing behaviour and mixing, but divides the IDU population into those that are susceptible to HIV infection (X), those that are recently HIV infected and are in the initial high viraemia acute phase of infection (*H*), those who have progressed to the lower viraemia phase of HIV (*Y*), those that are in the pre-AIDS high viraemia phase (Y2), and those that have AIDS (A). Susceptibles are infected at a per capita rate Π, upon which they enter the initial high viraemia phase of infection which has average duration 1/ς. They then enter the low viraemia phase of HIV infection (duration 1/γ), after which they enter the pre-AIDS high viraemia phase (duration 1/λ) and then onto AIDS (at rate ∆). The differential equations for the model are:

$$\frac{dX_i}{dt} = \Omega - X_i(\Pi_i + \mu)$$
$$\frac{dH_i}{dt} = \Pi_i X_i - H_i(\varsigma + \mu)$$
$$\frac{dY_i}{dt} = \varsigma H_i - Y_i(\gamma + \mu)$$
$$\frac{dY2_i}{dt} = \varphi Y_i - Y2_i(\lambda + \mu)$$
$$\frac{dA_i}{dt} = \lambda Y2_i - A_i(\Delta + \mu)$$

Equation 4

The force of infection Π_i has a similar form as for HCV:

$$\Pi_i = m_i \sum_{j=0,1} \frac{\rho_{ij}}{N_j}\left[H_j B_{1,j}^{hiv} + Y_j B_{2,j}^{hiv} + Y2_j B_{3,j}^{hiv}\right], \quad where \quad B_{e,j}^{hiv} = \left(1 - \left(1 - \beta_e^{hiv}\right)^{n_j}\right)$$

Equation 5

Appendix 2: Behavioural and epidemiological data collated for Bristol and Teesside

Behavioural model parameter	Bristol RDS	Bristol (7 city)	Teesside (7 city)
HCV prevalence overall	64.9%†	64.9%‡ (57.8-71.4%)	26.8% ‡ (20.7-33.5%)
HCV prevalence amongst injectors <=3 years	24.3%†	40.0% ‡ (19.1-63.9%)	13.6%‡ (5.2-27.4%)
HCV prevalence amongst injectors >3 years	70.9%†	67.6% ‡ (60.3-74.3%)	30.5%‡ (23.4-38.4%)
HIV prevalence	1%	1.0% ‡ (0.2-2.9%)	0% ‡ (0-1.8%)
Duration in years of injecting drugs (also **sweeting** - ~20 years for older IDUs and 11.4 in new IDUs)	11.7yrs	11.5yrs	7.7yrs
Injection frequency per week	14.5	24.5	18.0
Percentage of IDUs that have ever shared	>63%	59%	55%
Percentage of IDUs that share syringes in last 4 weeks	17.5%	32.5%	15.4%
Number of people syringe share from in last 4 weeks	1.8	2.0	1.7
Frequency of syringe sharing in last 4 weeks	-	5.6	2.85
Of those IDUs that syringe share:			
Percentage that share 1-4 times in last 4 weeks		62.5%	81.4%
Frequency of syringe sharing		2.1	1.8
Percentage that share >4 times in last 4 weeks		37.5%	18.6%
Frequency of syringe sharing		11.7	10.0
Percentage use filter/ mix container/mixing water/ that someone else used or share in last 4 weeks (RISKY)	>>33%	71.7%	59.3%
Number of times use last needle/syringe before disposal	1.9-2.4	4.6	3.7
OST intervention parameters			
Percentage currently on OST	67.5%	49.7%	76.2%
Average duration on OST in months	18-30* (Bristol data), ~10 (non-UK data) [75]		
% decrease in injecting/drug use – Cross sectional data	21.3%	36.5%	16.6%
Longitudinal data		50% [76]	
% decrease in syringe sharing rate– Cross sectional data	0%	50.0%	17.3%
Longitudinal data		66% (33-80%) [76]	
NSP intervention parameters			
New syringes used per week	14.6	22.0	15.3
Coverage of syringe distribution in last week – % of injections covered by a new syringe	109%	121%	106%
% of IDUs with less than 100% coverage	51.2%	54.9%	58.2%

% of IDUs with less than 50% coverage	23.6%	25.0%	25.4%
Ratio increase in syringe sharing rate if coverage <100%		1.39**	
>100%		0.67**	
Coverage and impact of combined interventions			
Percentage with coverage <100% and not on OST		36.6%	14.0%
Percentage with coverage >100% but not on OST		18.3%	8.5%
Percentage with coverage <100% but currently on OST		22.1%	44.0%
Percentage with coverage >100% and currently on OST		22.9%	33.5%
Ratio of mean syringe sharing rate if:			
Coverage <100% and not on OST**		2.05 (1.21-2.89)	
Coverage >100% and not on OST**		0.74 (0.49-1.19)	
Coverage <100% and on OST**		0.84 (0.43-1.05)	
Coverage >100% and on OST**		0.61 (0.36-0.86)	

† includes those that are RNA and antibody positive and all possible combinations. ‡ Includes only those that are antibody positive. *Estimated from reported duration on OST for IDUs that left from April to September 2006, and number that left in 6 month period.

**Because of small sample sizes this was estimated from the full 7 city data set

Appendix 3: Assessing the effectiveness of aspects of NSP intervention with respect to inclusion in an economic evaluation

Study	Brief summary and discussion	Model ?
Question 1		
Bluthental 2007	A cross sectional study examining the relationships between syringe coverage and a number of risk behaviours (e.g. receptive risk sharing). The main limitation with using the study for modelling purposes is that no intervention / technology is being evaluated, it is essentially descriptive. That is, the effects of specific interventions to increase access to syringe use are not evaluated	No, but threshold analysis
Question 2		
Fisher 2003	US RCT comparing NSP versus the option to purchase clean syringes from pharmacies. No differences in terms of risk behaviour outcomes were reported. The comparison of a free at the point of delivery NSP compared with private sales of injecting paraphernalia was not considered to be appropriate with respect to this project brief because syringes are currently free.	No
Masson 2007	A RCT comparing community- versus hospital-based NSPs in the USA. No differences were reported in terms of injection risk behaviours and only relatively brief descriptions of the services available at each site are provided. There are almost certainly to be a number of confounding factors affecting a direct comparison of the two NSP sites (eg. operating hours, and services offered at each location differed).	No
Rhodes 2004	A cross sectional study in a Russian city assessing the relationships between risky behaviour and source of injecting drug equipment. No intervention *per se* was evaluated, meaning it the study could not be used in the modelling exercise.	No
Miller 2002	A Canadian cross-sectional study assessing the relationship between risk taking behaviour and source of injecting materials eg pharmacies, fixed site and mobile NSPs. No differences in outcomes between	No

	the locations were reported, the services are poorly described and the usefulness of pharmacy sales as a comparator in the context of this report was not considered to be appropriate.	
Khoshnood 2000	A cross-sectional study examining the relationship between source of injecting paraphernalia (from a NSP or purchased from a pharmacy) and risk taking behaviour; performed in the USA. The study suggests that IDUs using the NSP were less likely 'to throw away' syringes compared with those who bought syringes at the pharmacies. No other differences in terms of risky behaviour were reported. The main limitation with this study is that the relevance of the comparator is considered to be outside the projects remit.	No
Tyndall 2002	A Canadian cohort study assessing the relationship between source of needles and 'trends' in distribution (that is, whether or not so called satellite needle distribution [SND] was undertaken). The results suggested that the presence of SND was generally associated with an increase in borrowing used equipment. However, even if it is believed that SND ultimately leads to poorer health outcomes, the study did not evaluate means of decreasing it. Thus the study does not include an evaluation of a health care technology *per se*.	No
Kral 2004	A US cross sectional study examining whether different syringe dispensing policies (in this case returns) impacted on risky behaviour. Three policies were evaluated 1) one old syringe for a new one, 2) one for a few new syringes 3) as many new syringes as requested. The only outcome that differed was that participants in 3) were less likely to reuse syringes compared with 1) and 2) combined. However, because it is difficult to quantify the risk of further HIV / HCV infection if a person reuses their own needles, it is not a particularly useful outcome to include in a model assessing the costs and benefits of preventing HIV / HCV infections through certain interventions. Equally problematic in terms of isolating the independent effects of the different policies is that the NSPs were open for different hours – and this was not taken into account in the multivariate analyses. Thus, it is impossible to know	No

	whether the decrease in syringe reuse in 3) was because more syringes were handed out per request, or because it was easier to request clean syringes at any given point in time or both. It is also understood that the UK-based NSPs generally already have a flexible approach to issuing sterile equipment. Thus, the value of assessing the cost-effectiveness of restricting this approach, was considered to be questionable.	
Bluthenthal 2004	A cross-sectional US study broadly examining whether NSPs and legal over the counter sales at pharmacies led to differences in risky behaviour. Almost no descriptions of the services were provided (not even the opening hours). The main thrust of the paper was examining whether different legal arrangements affected risky behaviour. No differences were reported in terms of syringe sharing.	No
Schilling 2004	A US cross-sectional study examining whether proximity to a NSP was associated with reduced risk taking behaviour. Distance from the NSPs was measured in terms of 'blocks'. There were a number of problems with trying to model this study, but perhaps the most important was that it did not evaluate a policy, it merely described a relationship between distance from a NSP and risky behaviour. Thus, even if a relationship was established, the question of how to improve access was not considered let alone evaluated.	No
Nelles 1997	A before and after study in a Swiss prison. Prison cohorts could not be modelled adequately using the existing model	No
Stark 2006	A German before and after study, assessing the effectiveness of access to vending machines providing sterile needles in a female prison, and social workers exchanging needles in a male prison. Outcomes were measured in terms of the needle sharing and the number of subsequent HIV / HBV /HCV infections. No real conclusions can be drawn about the number of infections prevented because of the study design, but there was a trend suggesting a decrease in sharing (71% in the 4 months prior to intervention and 11% at final follow-up). There were essentially three problems using this data for	No

	modelling purposes. First, the poor study design meant it was impossible to reasonably decide whether or not the interventions were effective. Second, it was not clear whether the vending machine, social workers or both were responsible for the reported trend. Lastly, the model as presently designed was not capable of modelling cohorts of prisoners.	
Obadia 1999	A French cross-sectional study assessing whether vending machines, dispensing sterile injecting equipment, was an effective adjunct to other approaches to promoting increased access to clean injecting equipment. Sterile syringes were available from vending machines, NSPs and through pharmacy sales. The results showed no differences in outcomes that could be incorporated into the model. The programmes were also poorly described (for example, it is unclear where the vending machines were located).	No
Rockwell 1999	A US cross-sectional study examining the relationship between distance from NSP, their use and frequency of risk taking behaviour. The results from the study suggest there is some reason to believe that IDUs living within 10 minutes walk of a NSP were less likely to report sharing injecting paraphernalia compared with those living further away. However, the study does not evaluate policies of improving attendance at NSPs.	No
Singer 1997	A US cross-sectional study assessing whether increased availability of sterile syringes and HIV education resulted in reduced risk taking behaviour and HIV seroprevalence over time. The study reports some evidence to suggest that the percentage of IDUs injecting with shared equipment was lowest amongst those that used both NSPs and pharmacy (sales) compared with those who didn't use either facility. However, no technology per se was addressed.	No
Question 3		
Strathdee 2006	A US-based RCT comparing different methods of encouraging IDUs visiting fixed and mobile NSPs to enter drug treatment programmes (ie OSTs). Specifically, the population referred to IDUs who were	Yes

	classed as ‘treatment seekers’. The intervention referred to allocation to a ‘case management model’. Whereas in the control arm, IDUs were only issued with a voucher indicating the date, time and location for attending an OST. The main outcome was measured in terms of the number of IDUs who turned up to their initial OST meeting within 7 days of referral from the NSP. There was no data capture after this point. The results indicate some advantage of the case management model over the control group. In terms of using these results for modelling purposes, the outcome measure is not particularly helpful. For example, it is not clear how many people in either trial arm actually received OST, nor is the duration of treatment or the longer term benefits of it. Also, it is not clear what was actually involved in the case management model, although it seems as though more contact with drug misuse staff and transport to the OST centre were important ingredients.	
Kidorf 2005	A US RCT examining the effectiveness of motivational interviewing (a 50 minute structured interview), job readiness schemes (for 50 minutes) and standard care as methods of increasing participation in OSTs. Follow-up was one year and the main outcome assessed was enrolment into OST treatment. In terms of its suitability for modelling, some description is provided of the interventions and the control arm, but no differences were seen in terms of outcomes.	No
Pollack 2002	A US cohort study, examining the impact of a health care van in reducing emergency department visits. The people on the van administered general health advice, acute and minor medical care, prescription refills and other health care services. The health care van was associated with lower rates of hospital admissions due, compared with it not being available, but no other outcomes were assessed (such as change in risk taking behaviour), thus it is not clear whether the intervention had any impact HIV and HCV infection rates. The services provided by the van / staff are also poorly	No

	described.	
Sears 2001	A US cross sectional study assessing whether homeless IDUs having contact with a NSP designed by peers, that included 'community level activities' and open for longer hours, were more likely to engage in risky injecting behaviour compared with 'comparison NSPs'. There was some evidence to suggest that the intervention site was more effective in terms of reducing syringe use, however there were three problems in terms of modelling the cost-effectiveness of these interventions. First, they are poorly described. Second they effectively appear to include more than one potentially important attribute of care (for example, the peer designed programmes were open for longer hours and were implemented by peers - thus individual treatment effects are confounded). Third, the model is not currently capable of modelling homeless cohorts.	No
Tyndall 2002	This is a Canadian cohort study essentially assessing the relationship between satellite needle distribution (SND) and the likelihood of needle distribution. The results from the study suggest that there might be a relationship between SND and an increase likelihood of borrowing used injection equipment. However, even if these results are believed, the study did not evaluate methods to reduce it.	No
Valente 2001	A US cross sectional study assessing the relationship between attendance at a NSP and syringe relay (returning a syringe originally provided for someone else). The results from the study suggest that lower users of NSPs were more likely to return syringes originally issued to someone else compared with higher users of the service, and that they would do so more quickly. However, even if these results are considered to be accurate, no system of increasing the number of syringes and the speed at which this was done was evaluated.	No
Huo 2005	A US cross-sectional study examining the relationship between risky behaviour and source of injecting paraphernalia. The results from the study suggest that IDUs who reported always receiving needles	No

	from a NSP personally were less likely to share needles compared with people who obtained at least some needles from other sources. Other improved outcomes were also positively associated with receiving needles directly from NSPs. However, the problem with using these results for the modelling exercise was that no policy of increasing NSP contact was studied or evaluated.	
Question 4		
Van den Berg 2007	A Dutch cohort study examining the impact of harm reduction programmes on HIV and HCV infection rates. The study has a 20-year length of follow up, and contains a relatively large sample size. The analysis suggests that IDUs prescribed OST (methadone) were associated with a lower incidence of HIV and HCV infection. There was also some evidence to suggest that methadone dose and contact with a NSP (combined) were associated with a reduction in HIV / HCV seroconversion rates. However, methods of increasing access / encouraging attendance at NSPs and to OST treatments were not evaluated.	No