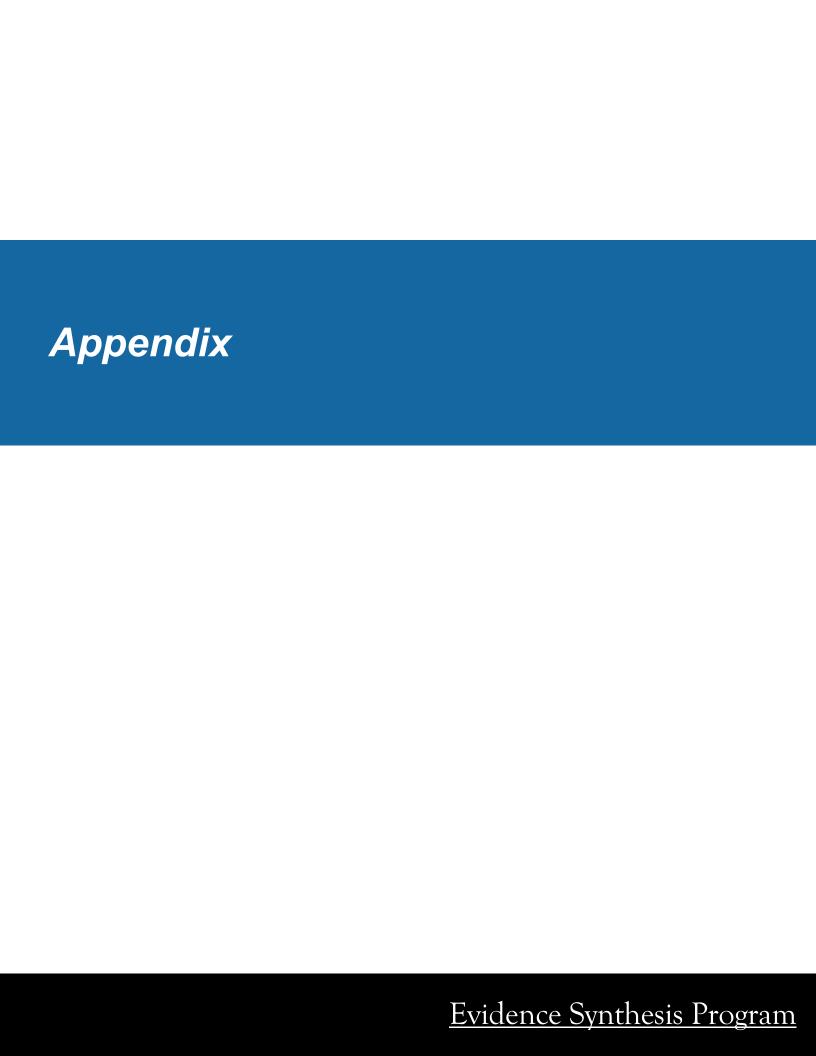
Effectiveness of Syringe Services Programs

December 2023



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SEARCH STRATEGIES

| Search Date: 03/01/23 | | Search Statement | Results |
|-----------------------|---|--|---------|
| Ovid MEDLINE | 1 | Needle-Exchange Programs/ or (((needle* or syringe*) adj2 (exchange* or program* or service*)).ti,ab,kf. | 3566 |
| | 2 | limit 1 to English language | 3342 |
| CINAHL | 1 | (MH "Needle Exchange Programs") OR TI (((needle* OR syringe*) N2 (exchange* OR program* OR service*))) | 2175 |
| | 2 | limit 1 to English language | 2162 |
| PsycINFO | 1 | Needle Exchange Programs/ or ((needle* or syringe*) adj2 (exchange* or program* or service*)).ti,ab. | 1506 |
| | 2 | limit 1 to English language | 1430 |
| Cochrane Database of | 1 | MeSH descriptor: [Needle-Exchange Programs] this term only | 44 |
| Systematic Reviews | 2 | (((needle* or syringe*) NEAR/2 (exchange* or program* or service*)) or (supervis* NEAR/2 injecti* NEAR/2 (center* or centre* or facilit*))):ti,ab,kw | 195 |
| | 3 | limit 3 to reviews | 2 |
| | 4 | limit 4 to english language | 2 |
| | 5 | limit 5 to last 7 years | 2 |
| | | Total | 6,936 |
| | | Total after deduplication | 3,743 |



STUDIES EXCLUDED DURING FULL-TEXT SCREENING

| Citation | Exclude Reason |
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| Citation | Exclude Reason |
|---|-----------------------------|
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| Citation | Exclude Reason |
|---|-----------------------------|
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UNDERWAY STUDIES

Citation

NCT02654366. Community Supported Risk Reduction for Syringe Exchange Participants. CN-01555077. https://clinicaltrials.gov/show/NCT02654366.

NCT01557998. Testing and Linkage to Care for Injecting Drug Users in Kenya. CN-01591363. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01591363/full.



CHARACTERISTICS OF INCLUDED PRIMARY STUDIES

| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|-------------------------------|---------------------------|--------------------------|---|---|---|---|
| RCTs | | | | | | |
| Braback 2016 ⁸⁵ | Skane Sweden | N=75 NR | Mean age: 37 % Male: 73 Race/ethnicity NR | Heroin | SSP clients receiving a strength- based case management intervention to facilitate treatment referral compared to SSP clients receiving referral only | Linkage to treatment/utilization of referred services ^a |
| Fisher 2003 ³ | Alaska US | N=600 12 mos | Mean age: 39 % Male: 76 % AA/Black: 19 % Native American: 20 % Other: 5 % White: 56 | Heroin, cocaine, speedball, other opioids, amphetamines | Randomized to SSP access or training on acquiring needles from pharmacies | Injection frequency |
| Lewis 2015 ^{b 29} | New York, NY US | N=592 3 mos | Mean age: 44 % Male: 69 % AA/Black: 29 % Hispanic: 51 % White: 16 | NR | Pharmacies that received harm reduction training and provided additional services compared to pharmacies providing usual care | Unsafe disposal of syringes |
| Cohort Studies | | | | | | |
| Brooner 1998 ^{28,87} | Baltimore, MD US | N=325 1 yr | Mean age: 38 % Male: 50 % White: 41 | Heroin, cocaine, sedative, cannabis | Referred to OAT from SSP compared to other referral sources | Linkage to treatment/utilization of referred services |
| Hagan 2000 ⁴ | Seattle, WA US | N=Variable 1 yr | Age NR % Male: 62 % AA/Black: 20 % Other: 11 % White: 69 | Heroin, speedball, cocaine, amphetamines | Current exchange users, new exchange users, ex-exchangers compared to never exchangers | Injection frequency, linkage to treatment/utilization of referred services |
| Hartgers 1989 ⁵ | Amsterdam, Netherlands | N=54 Mean 13.5 mos | Mean age: 32 % Male: 70 NR | Heroin, cocaine, methadone, hashish, marijuana, tranquillizers, amphetamines | Regular exchangers (used SSP > 90% of the time) compared to irregular exchangers or non-exchangers | Injection frequency, linkage to treatment/utilization of referred services |
| Huo 2006 ⁹ | Chicago, IL US | N=707 3 yrs | Mean age: 40 % Male: 71 % AA/Black: 44 % Non-AA/Black: 55 | Heroin, speedball, powder/crack cocaine | SSP users (used SSP at least twice ever and enrolled for at least 30 days) compared to non-SSP users | Injection frequency |



| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|------------------------------------|-----------------------|-----------------------------|---|---|--|---|
| Kuo 2003 ²⁶ | Baltimore, MD US | N=163 3 mos | Mean age: 43 % Male: 68 % AA/Black: 99 | Heroin, cocaine | Duration and frequency of SSP use | Linkage to treatment/utilization of referred services |
| Latkin 2006 ²⁵ | Baltimore, MD US | N=440 Average 15 mos | 57% age >39 yrs % Male: 68 % AA/Black: 94 | Heroin, speedball, powder/crack cocaine | Current SSP utilization (past 6 mo) compared to no SSP use | Linkage to treatment/utilization of referred services |
| Marmor 2000 ⁶ | New York, NY US | N=328 Median 29.7 mos | Mean age: 40 % Male: 78 29% AA/Black: 29 % Asian: <1 % Hispanic: 28 % Native American: <1 % Other: <1 % White: 42 | Heroin, powder/crack cocaine, marijuana | Consistent or sporadic SSP users compared to no SSP use | Injection frequency |
| Monterroso 2000 ⁷ | Multiple US | N=2,306 Mean 7.8 mos | Mean age: 38 % Male: 63 % AA/Black: 43 % Hispanic: 32 % White: 21 | NR | Ever used an SSP compared to never used an SSP | Injection frequency |
| Schoenbaum 1996 ⁸ | New York, NY US | N=329 5 yrs | Median age: 30 % Male: 65 % Black: 17 % Hispanic: 67 % White: 16 | Heroin, cocaine, speedball | Ever used an SSP compared to never used an SSP | Injection frequency |
| Strathdee 1999 ^{27,86} | Baltimore, MD US | N=1,483 4.5 yrs | Median age: 40 % Male: 74 % AA/Black: 95 % Non-AA/Black: 5 | Heroin, cocaine, speedball | SSP attendance compared to no attendance | Linkage to treatment/utilization of referred services |
| Pre-Post Studies | | | | | | |
| Bartholomew 2021 ¹⁰ | Miami, FL US | N=115 Variable | Median age: 38 % Male: 77 % Hispanic: 45 % Non-Hispanic Black: 4 % Non-Hispanic White: 50 | Heroin, powder/crack cocaine, methamphetamine, speedball, fentanyl | SSP clients | Injection frequency |



| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|------------------------------------|-------------------------|--------------------------|--|---|--|--|
| Cox 2000 ¹¹ | Ireland | N=370 3 mos | Mean age: 23 % Male: 79 Race/ethnicity NR | Heroin | SSP attendance | Injection frequency, linkage to treatment/utilization of referred services |
| Donoghoe 1989 ¹² | England and Scotland | N=142 Variable | Mean age: 30 % Male: 86 Race/ethnicity: NR | Heroin, methadone, amphetamine, cocaine, barbiturates, tranquillizers, others | Attendance at an SSP at least once during the 1 year period prior to the study | Injection frequency |
| Iversen 2013 ¹³ | Multiple Australia | N=724 Variable | Mean age: 32 % Male: 65 Race/ethnicity NR | Methamphetamine, heroin, cocaine, methadone or buprenorphine, pharmaceutical opioids, others | SSP users across 3 time periods | Injection frequency |
| Patel 2018 ¹⁴ | Indiana US | N=148 Median 10 wks | Median age: 34 % Male: 56 % Non-Hispanic White: 98 % Other: 2 | Opana, heroin, methamphetamines, others | SSP clients at first and most recent visit to the SSP | Injection frequency |
| Schechter 1999 ¹⁵ | Vancouver Canada | N=694 6 mos | Median age: 36 % Male: 68 % Aboriginal: 25 % Other: 10 % White: 65 | Heroin, cocaine | Frequent SSP attendance compared to no attendance | Injection frequency |
| Vertefeuille 2000 ¹⁶ | Baltimore, MD US | N=112 6 mos | Mean age: 40 % Male: 71 % AA/Black: 89 % Other: 11 | Heroin, cocaine, speedball | SSP enrollees | Injection frequency, linkage to treatment/utilization of referred services, unsafe disposal of syringes |
| Vlahov 1997 ¹⁷ | Baltimore, MD US | N=422 6 mos | Mean age: 38 % Male: 67 % AA/Black: 87 | Heroin, speedball, cocaine | SSP enrollees | Injection frequency, linkage to treatment/utilization of referred services, unsafe disposal of syringes |
| Vogt 1998 ¹⁸ | Hawaii US | N=208 <i>NR</i> | NR | NR | SSP attenders | Injection frequency |



| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|--|----------------------------|--------------------------|--|--|--|---------------------------------|
| Cross-Sectional St | tudies | | | | | |
| Allen 2021 ²⁰ | Cabell County, WV US | N=420 <i>NA</i> | Mean age: 36 % Male: 61 % Non-Hispanic White: 84 | Heroin, fentanyl, buprenorphine or Suboxone, prescription opioid, crystal methamphetamine, speedball, cocaine | Acquired sterile syringes from an SSP in the past 6 mos compared to those who did not | Naloxone distribution or use |
| Bluthenthal 2004 ^{32,107} | Multiple US | N=584 <i>NA</i> | Mean age: 41 % Male: 58 % AA/Black: 41 % Hispanic: 38 % Other: 2 % White: 18 | Heroin, speedball, amphetamine, powder/crack cocaine | Residence in cities with more permissive exchange policies compared to residence in city with less permissive exchange policy | Unsafe disposal of syringes |
| Cleland 2007 ³⁰ | New York US | N=1,030 <i>NA</i> | Mean age: 37 % Male: 72 % AA/Black: 13 % Hispanic: 77 % White: 11 | Heroin, powder/crack cocaine | Obtained syringe used for last injection from SSP or source related to ESAP (<i>ie</i> , pharmacy, hospital, clinic, doctor) compared to other source | Unsafe disposal of syringes |
| Coffin 2007 ³³ | Multiple US | N=680 <i>NA</i> | Mean age: 42 % Male: 62 % AA/Black: 59 % Hispanic: 21 % Other: 9 % White: 12 | Heroin, powder/crack cocaine | Ever used an SSP or safe syringe source compared to never used an SSP or unsafe syringe source | Unsafe disposal of syringes |
| Cotton-Oldenburg 2001 ³¹ | Minnesota US | N=570 <i>NA</i> | Mean age: 37 % Male: 66 % AA/Black: 36 % American Indian: 9 % Asian: 1 % Hispanic: 14 % Other: 3 % White: 37 | Heroin, cocaine, speedball, methamphetamine, others | Time period (9-12 mos) before and after legislation allowing for legal sale of syringes by pharmacies without a prescription | Unsafe disposal of syringes |
| Dasgupta 2019 ³⁴ | Indiana US | N=200 <i>NA</i> | 18-25: 13% 25-34: 35% 35-44: 31% ≥45: 31% % Male: 58 % Hispanic: 2 | Opana, methamphetamine, heroin, other prescription opioid | Time period before and after start of large-scale public health response to HIV outbreak including establishment of SSP | Unsafe disposal of syringes |



| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|---------------------------------|----------------------------|--------------------------|---|--|--|---|
| | - | - | % Multiracial: 5 % White: 92 | | | |
| Jones 2021 ²¹ | Baltimore, MD US | N=263 <i>NA</i> | 18-44: 42% ≥45: 58% % Male: 70 % AA/Black: 61 % White: 39 | Heroin, speedball, marijuana tranquilizer | Registered SSP client compared to non-client peers | Naloxone distribution or use, knowledge of overdose risk |
| Khoshnood 2000 ³⁵ | New Haven, CT US | N=373 <i>NA</i> | Mean age: 40 % Male: 64 % AA/Black: 37 % Hispanic: 16 % White: 44 | Heroin | Usual syringe source SSP, pharmacy, or both during past 6 mos compared to other source | Unsafe disposal of syringes |
| Kim 2021 ²⁴ | San Francisco, CA US | N=458 <i>NA</i> | Mean age: 46 % Male: 68 % AA/Black: 26 % Asian/Pacific Islander: 7 % Hispanic: 15 % Native American/Alaska Native: 16 % White: 67 | Opioid, methamphetamine | Received needles or syringes from an SSP in the past 12 mos compared to not receiving needles or syringes from SSP | Knowledge of overdose risk |
| Quinn 2014 ³⁶ | Los Angeles, CA US | N=412 <i>NA</i> | Median age: 50 % Male: 69 % AA/Black: 30 % Hispanic: 41 % Other: 9 % White: 21 | Heroin, powder/crack cocaine, methamphetamine, tranquilizers, opiates, methadone | Primary source of syringes past 12 mos SSP or pharmacy compared to other source | Unsafe disposal of syringes |
| Reed 2019 ²² | Philadelphia, PA US | N=571 <i>NA</i> | Median age: 35 % Male: 78 % AA/Black: 12 % Hispanic: 21 % Other: 3 % White: 64 | Heroin, speedball, powder/crack cocaine, methamphetamine, opioid analgesics, benzodiazepines | Primary source of syringes past 6 mos SSP compared to pharmacy or other source in the past 12 mos | Naloxone distribution or use |
| Riley 2010 ³⁷ | San Francisco, CA US | N=105 <i>NA</i> | Median age: 42 % Male: 67 % AA/Black: 14 % Hispanic: 12 | Heroin, methamphetamine/speed | Obtained syringes from an SSP or pharmacy in the past 30 days compared to not obtaining syringes from an SSP or pharmacy in the past 30 days | Unsafe disposal of syringes |



| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|---------------------------------------|-----------------------|---|---|---|--|---------------------------------|
| | | | % Other: 18 % White: 51 | | | |
| Sherman 2004 ³⁸ | Baltimore, MD US | N=294 <i>NA</i> | Median age: 25 % Male: 58 % AA/Black: 30 % Other: 3 % White: 67 | Heroin, powder/crack cocaine | Safe acquisition of syringes (primarily obtaining syringes from an SSP or pharmacy) compared with unsafe acquisition of syringes (primarily obtaining syringes from other sources) past 6 mos | Unsafe disposal of syringes |
| Spring 2022 ²³ | Multiple UK | N=2,139 <i>NA</i> | Mean age: 40 % Male: 72 Race/ethnicity: NR | Heroin, benzodiazepines, others | Past-year contact with SSP compared to no past-year contact with SSP | Naloxone distribution or use |
| Turner-Bicknell 2021 ¹⁹ | Ohio US | N=NR <i>NA</i> | NR | NR | Before and after implementation of a needs-based distribution model | Naloxone distribution or use |
| Wood 2003 ³⁹ | Vancouver Canada | N=587 <i>NA</i> | Median age: 39 for SSP users; 40 for non-SSP users % Male: 61 % Aboriginal: 32 % non-Aboriginal: 68 | Heroin, cocaine | Use of all-night SSP in past 6 mos (includes people who used the city's fixed exchange sites) compared to non-use of SSP | Unsafe disposal of syringes |
| Zlotorzynska 2018 ⁴⁰ | Multiple US | N=6,321 <i>NA</i> | Mean age: 43 % Male: 72 % non-Hispanic White: 45 % Other: 55 | Heroin, speedball, powder/crack cocaine, methamphetamines, prescription opioids, others | Primary syringe source SSP compared to pharmacy past 12 mos | Unsafe disposal of syringes |
| Ecological Studies | 3 | | | | | |
| Broadhead 1999 ⁴⁴ | Connecticut US | N=NA <i>NA</i> | NA | NR | Time period during operation of an SSP compared to time period following closure of the SSP | Unsafe disposal of syringes |
| Cooper 2012 ⁴⁸ | New York, NY US | N=42 health districts NA | NA | NR | SSP access (percent of each district's surface area within 1 mile of an SSP site) or access to pharmacies selling syringes by study year | Neighborhood crime rates |
| Doherty 1997 ^{45,88} | Baltimore, MD US | N=32 city blocks 2 yrs | NA | NR | 1 and 2 mos after SSP initiation compared to time prior to SSP initiation | Unsafe disposal of syringes |
| Fuller 2002 ⁴⁶ | New York, NY US | N=27 blocks and 10 pharmacies NA | NA | NR | Time period before and after enactment of ESAP (legal pharmacy sale of syringes without a prescription) | Unsafe disposal of syringes |



| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|---------------------------|-----------------------|--------------------------|---|------------------------------------|---|--------------------------------|
| Marx 2000 ⁴⁹ | Baltimore, MD US | N=NA NA | NA | NR | Program areas (within 0.5-mile radius of SSP site) before and after establishment of SSPs and compared to non-program areas | Neighborhood crime rates |
| Oliver 1992 ⁴⁷ | Portland, OR US | N=NA <i>NA</i> | NA | NR | Immediate vicinity of an SSP before and after establishment | Unsafe disposal of syringes |
| Ecological and C | ross-Sectional Stu | dies | | | | |
| Levine 2019 ⁴¹ | Miami, FI US | N=930 <i>NA</i> | 18-29: 12.7% 30-39: 26.3% 40-49: 27.9% ≥50: 33.3% % Male: 78 % Asian or Pacific Islander: 1 % Hispanic: 40 % Multiple races/Other: 1 % Native American: 2 % non-Hispanic Black: 32 % non-Hispanic White: 26 | NR | City residence pre- and post- implementation of the SSP | Unsafe disposal of syringes |
| Tookes 2012 ⁴² | Multiple US | N=1,050 <i>NA</i> | San Francisco: 18-29: 6% 30-39: 18% 40-49: 41% ≥50: 35% % Male: 73 % Asian or Pacific Islander: < 1 % Hispanic: 10 % Multiple races/Other: 5 % Native American: 4 % non-Hispanic Black: 37 % non-Hispanic White: 44 Miami: 18-29: 8% 30-39: 20% 40-49: 31% | NR | City with an SSP and residents of city with an SSP compared to city without an SSP and residents of city without an SSP | Unsafe disposal of syringes |
| | | | 40-49. 31% ≥50: 45% % Male: 79 % Asian or Pacific Islander: 1 | | | |



| Study | City/State Country | Sample Size Follow-up | Participant Characteristics | Non-Prescribed Substance(s) Use | Intervention/Exposure and Comparator (if applicable) | Included Outcome(s) |
|---------------------------|-----------------------|--------------------------|-----------------------------|------------------------------------|--|------------------------|
| | | | % Hispanic: 40 | | | |
| | | | % Native American: 1 | | | |
| | | | % non-Hispanic Black: 36 | | | |
| | | | % non-Hispanic White: 23 | | | |
| Wenger 2011 ⁴³ | San Francisco, | N=602 | NR | NR | Syringe source SSP or pharmacy | Unsafe disposal of |
| • | CA | NA | | | prior 6 mos compared to other | syringes . |
| | US | | | | source | |

Notes. ^a This study was included for a comparison relevant to KQ1a; ^b Data for the outcome of interest were cross-sectional.

Abbreviations. AA=African-American; AIDS=acquired immunodeficiency syndrome; ESAP=Expanded Syringe Access Demonstration Program; HIV=human immunodeficiency virus; MMT=methadone maintenance treatment; mos=months; NA=not applicable; NR=not reported; OAT=opioid agonist therapy; RCT=randomized controlled trial; SSP=syringe services program; wks=weeks.



RISK OF BIAS ASSESSMENTS

RANDOMIZED CONTROLLED TRIALS (ROB-2)

| Trial Name or Author Year | Bias from randomization process | Bias from deviation from intended interventions (Assignment) | Bias from deviation from intended interventions (Adherence) | Bias from missing outcome data | Bias in measurement of outcome | Bias in selection of reported result | Overall risk of bias (Low, Some concerns, High) |
|------------------------------|--|--|---|--|--|--------------------------------------|---|
| Braback 2016 ⁸⁵ | Low Computer generated block randomization with allocation concealed | Some concerns Participants were likely unblinded, unclear if carers were blinded. Unclear if there were deviations in intervention. | Some concerns Participants were likely unblinded, unclear if carers were blinded. Intervention occurred right after initial assessment, so likely adhered to. | Low Low number of dropouts and regarded as non- attenders | Low Outcome measured as showing up for treatment in both groups. | Low Main outcome reported | Some concerns |
| Fisher 2003 ³ | Low Concealed randomization by a separate person | Some concerns Patients and intervention administrators unblinded at time of giving intervention. Unclear if there were deviations in intervention. | Some concerns Participants were likely unblinded, unclear if carers were blinded. Intervention occurred right after initial assessment, so likely adhered to. | Some concerns Unclear what the "305 complete observations" in the GLM corresponds to in terms of patients assessed. 81% had at least 1 follow-up. No difference in baseline variables between those who completed at least 1 follow-up and those completely lost to follow-up. | Some concerns Injection frequency assessed by RBA in interview, potential for recall bias based on intervention. | Low Main outcome reported | Some concerns |

Abbreviations. GLM=generalized linear model; RBA=Risk Behavior Assessment.

COHORT STUDIES (ROBINS-I)

| Study Name or Author Year | Bias due to confounding | Selection bias | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to measurement of outcomes | Bias due to missing data | Bias in the selection of reported results | Overall risk of bias (Low, Moderate, Serious, Critical, No Information) |
|---|-------------------------|--|---|---|---|--|---|--|
| Brooner 1998; ²⁸ Neufeld 2008 ⁸⁷ | | Low Includes all who presented for treatment during timeframe. | Low Intervention classified as referral source | Low "Intervention" is referral source, so likely no overlap/departures. | Low Retention in treatment objective measurement. Drug | Low Missing data for urinalysis results only. Analyses conducted without missing | Low All prespecified results appear to be reported. | Unclear |



| Study Name or Author Year | Bias due to confounding | Selection bias | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to measurement of outcomes | Bias due to missing data | Bias in the selection of reported results | Overall risk of bias (Low, Moderate, Serious, Critical, No Information) |
|------------------------------|--|--|--|--|--|---|---|--|
| | disorders), but likely some residual confounding based on high # of differences at baseline in measured variables. | | before treatment started. | | use confirmed by urinalysis. | data and coding all missing as "positive." | | |
| Hagan 2000 ⁴ | Unclear Differences between | Low Includes sample | Low Classified SSP | Low Classification of | Low Standard | Unclear 78% completed | Low All prespecified | Unclear |
| | groups in injection characteristics, adjusted for different variables in different | of IDUs from several recruitment points over time. | use over follow- up period into distinct categories based | SSP use over time captures changes in use over the follow-up period. | questionnaire administered by trained interviewers at all time points. | follow-up and were included in sample, unclear if any differences | results appear to be reported. | |
| | analyses. | points over time. | on when SSP use started/stopped. | топоw-up ретгой. | at all time points. | between those without follow-up. | | |
| Hartgers 1989 ⁵ | Unclear Differences between groups at baseline in injecting and treatment variables. Includes a logistic regression controlling for some variables for borrowing outcome at first interview. | Low Includes SSP attenders and non-attenders from same geographical region during recruitment. | Low Classified SSP use over follow- up period into distinct categories based on SSP use. | Low Classification of SSP use over time captures changes in use over the follow-up period. | Low Standard questionnaire administered by trained interviewers at all time points. | High 41% completed second interview, others omitted from follow-up analysis. | Low All prespecified results appear to be reported. | High |
| Huo 2006 ⁹ | Unclear Unclear baseline differences between groups, but did adjust for injecting variables, drug treatment, and age. | Unclear One SSP site had different recruitment start and follow-up duration. Adjusted for follow-up duration in analyses. Non- SSP users recruited by different people than SSP users. | Low Classified by SSP use, which was based off neighborhood. Excluded small percentage of participants in neighborhood w/o SSP who travelled to SSP. | Unclear Does not appear to account for starting/stopping SSP use over follow-up period. | Low Standard questionnaire administered by trained interviewers at all time points. | Unclear Excluded participants without at least 1 follow-up (17%), but attrition analysis showed no difference between groups in baseline injection frequency. | Low All prespecified results appear to be reported. | Unclear |
| Kuo 2003 ²⁶ | Unclear Baseline variables by SSP use not reported but does | Low Includes all referred to LAAM program, | Unclear All patients were enrolled in SSP but classifies use | Low Accounts for changes in SSP use by using a | Unclear Doesn't specifically describe how SSP | Unclear Describes level and management of | Low | Unclear |



| Study Name or Author Year | Bias due to confounding | Selection bias | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to measurement of outcomes | Bias due to missing data | Bias in the selection of reported results | Overall risk of bias (Low, Moderate, Serious, Critical, No Information) |
|---------------------------------|---|--|---|--|---|--|---|--|
| | adjust for some demographics and other variables. | except for a small proportion who did not have SSP data. | as number of visits per month. | variable of "# SSP visits per month." | visit data was collected. | missing urinalysis data, but level and handling of missing data for other variables not described. | All prespecified results appear to be reported. | |
| Latkin 2006 ²⁵ | Unclear | High | Low | Unclear | Low | Unclear | Low | High |
| | Baseline variables by SSP use not reported but does adjust for demographics and drug use variables. | Appears that 30% without follow-up data were excluded from the study, but unclear proportion among IDUs. | Classified as SSP use within the past 6 months in standard survey responses. | New use of SSP or stopping SSP use during follow-up does not appear to be evaluated. | Standard questionnaire administered by trained interviewers at all time points. | Excluded participants without follow-up, handling of other missing data not described. | All prespecified results appear to be reported. | |
| Marmor 2000 ⁶ | High Unclear differences at baseline between SSP users and non- users and no adjustment for any variables. | High Excluded 45% of eligible participants without 4 interviews. Did not differ on most variables but did differ in age and use of methadone maintenance and shooting galleries. | Low Classified SSP users by use over time. | Low Classification of SSP use over time captures changes in use over the follow-up period. | Low Interviewer- administered questionnaires at all visits. | Unclear Excluded participants without 4 follow- up visits, handling of other missing data not described. | Low All prespecified results appear to be reported. | High |
| Monterroso 2000 ⁷ | Unclear | Low | Unclear | Unclear | Low | High | Low | High |
| | Unclear differences at baseline between SSP users and non- users. Unclear if SSP use analysis is adjusted. | Includes sample of IDUs from several recruitment points over time period. | Question around SSP use and classification of use not well described. | Mentions "consistent users" reported SSP use at 2 visits, but other classification of changes over time not described. | Interviewer- administered questionnaires at all visits. | Excluded 39% of participants that did not have follow-up. Similar on most characteristics, but more likely to be homeless. | All prespecified results appear to be reported. | |
| Schoenbaum 1996 ⁸ | High Differences at baseline in drug use treatment, no adjustment for any | Low Includes sample of IDUs recruited over time period. | Unclear Classified as "ever" using SSP or "never" using SSP based on interviews, but | Low Classification of SSP use over time captures changes | Low Interviewer- administered questionnaires at all visits. | High For prospective analyses excluded 36% | Low All prespecified results appear to be reported. | High |



| Study Name or Author Year | Bias due to confounding | Selection bias | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to measurement of outcomes | Bias due to missing data | Bias in the selection of reported results | Overall risk of bias (Low, Moderate, Serious, Critical, No Information) |
|--|---|--|--|--|---|---|---|--|
| | confounders for outcome analyses. | | intervention changed from illegal SSP to legal SSP over study period. | in use over the follow-up period. | | without full follow-up data. | | |
| Strathdee 1999; ²⁷ Shah 2000 ⁸⁶ | Unclear Baseline variables by SSP use not reported but does adjust for demographics and drug use variables. | High Excluded 50% of original sample who did not inject from enrollment to post-SSP timeframe, but initial inclusion criteria required drug use from 1977. | Unclear SSP variable not well described, unclear if it is any visit over the timeframe. | Unclear SSP variable not well described, unclear if it accounts for potential changes in SSP use over time. | Low Interviewer- administered questionnaires at all visits. | Unclear Individuals who were lost to follow-up were censored. Unclear how many (says "ie, 10%" but unclear if this is the actual % that were censored). | Low All prespecified results appear to be reported. | High |

Abbreviations. IDU=injection drug user; LAAM=levomethadyl acetate hydrochloride; SSP=syringe services program.

UNCONTROLLED PRE-POST STUDIES (ROBINS-I)

| Study Name or Author Year | Bias due to confounding | Selection bias | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to measurement of outcomes | Bias due to missing data | Bias in the selection of reported results | Overall risk of bias (Low, Moderate, Serious, Critical, No Information) |
|--------------------------------|--|---|---|---|---|--|---|--|
| Bartholomew 2021 ¹⁰ | Unclear Used GEE to account for some potential confounders but did not have multiple pre- intervention measurements. | High Only included 12% of total cohort with 2 follow-up assessments, differences between baseline and follow-up groups. | Low Timepoints based on assessments completed at SSP. | Unclear Time between assessments varied and was based on SSP use. | Low Methods of data collection similar across timepoints after initial enrollment. | Unclear Excluded participants without 2 visits, level of other missing data unclear. | Low All relevant outcomes appear to be reported. | High |
| Cox 2000 ¹¹ | High Single initial measurement, no adjustment for time trends. | Unclear Only included 28% of those invited to participate. Unclear how many completed baseline and no | Low Timepoints based on initial and follow-up visits. | Unclear Defines follow-up at 3 months, but unclear adherence to this timing for all participants. Unclear | Low Structured questionnaires by trained interviewers at both timepoints. | Unclear Missing data appear to be excluded from analyses for individual outcomes. | Low All relevant outcomes appear to be reported. | High |



| Study Name or Author Year | Bias due to confounding | Selection bias | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to measurement of outcomes | Bias due to missing data | Bias in the selection of reported results | Overall risk of bias (Low, Moderate, Serious, Critical, No Information) |
|------------------------------|---|---|---|---|--|---|---|--|
| | | follow-up and unclear differences between those included and excluded. | | frequency of SSP use. | | | | |
| Donoghoe 1989 ¹² | High Single initial measurement, no adjustment for time trends, and comparison group of non- attenders showed differences. | High Only included 6% of the initial cohort, differences between those who completed 2nd interview and those who did not. | Low Timepoints based on initial and follow-up visits. | Unclear Defines follow-up at 2-4 months, but unclear adherence to this timing for all participants. Unclear frequency of SSP use. | Low Structured questionnaires by staff at both timepoints. | Unclear Excluded participants without 2 visits, level and handling of other missing data unclear. | Low All relevant outcomes appear to be reported. | High |
| Iversen 2013 ¹³ | Unclear Appears only to have adjustment for HCV incidence outcome. Accounts for time trends by creating separate groups by timeframe. | High Excluded high proportion of original sample without matching. Included 60% of the matched sample with negative HCV tests. Differences between those included and excluded. | Low Timepoints based on repeat surveys and had to be within 1-year. | Unclear Follow-up had to be within 1-year, but unclear how variable time between records was. Unclear frequency of SSP use. | Low Same survey used at all time points. | Unclear Out of original sample, excluded 17% without full data. | Low All relevant outcomes appear to be reported. | High |
| Patel 2018 ¹⁴ | Unclear Single initial measurement, but timeframe within about 1 year. | Unclear Included 62% of original sample with at least 2 visits. Unclear differences between those included and excluded. | Low Timepoints based on visits and had to be at least 7 days apart. | Unclear Follow-up had to be at least 7 days apart, but unclear how variable time between surveys was. Unclear frequency of SSP use. | Low Structured questionnaires by staff at both timepoints. | Low Mentions missing data on only 2 participants. | Low All relevant outcomes appear to be reported. | Unclear |
| Schechter 1999 ¹⁵ | Unclear Single initial measurement, no adjustment for time trends but injection frequency | Unclear Included 80% of original sample with 1 follow-up visit. Unclear differences between those | Low Timepoints based on initial and follow-up visits. | Unclear Unclear how timing of follow- up varied across participants. Classified frequent and | Low Structured questionnaires by staff at both timepoints. | Unclear Unclear level and handling of missing data. | Low All relevant outcomes appear to be reported. | Unclear |



| Study Name or Author Year | Bias due to confounding | Selection bias | Bias in classification of interventions | Bias due to departures from intended interventions | Bias due to measurement of outcomes | Bias due to missing data | Bias in the selection of reported results | Overall risk of bias (Low, Moderate, Serious, Critical, No Information) |
|---------------------------------|---|--|--|---|---|---|---|--|
| | outcome analysis limited to post- need exchange timeframe. | included and excluded. | | infrequent SSP users. | | | | |
| Vertefeuille 2000 ¹⁶ | Unclear Single initial measurement, no adjustment for time trends, but timeframe within 6 months. | Unclear Every 7th enrollee invited, differences between those enrolled and not enrolled in some demographics and drug use variables. | Low Timepoints based on initial and follow-up visits. | Unclear Follow-up at 6 months, but unclear frequency of SSP use. | Low Structured questionnaires by staff at both timepoints. | High Only had follow- up data for 52% of enrollees. Drug injection frequency analysis limited to those with follow- up and who were HIV positive at baseline. | Low All relevant outcomes appear to be reported. | High |
| Vlahov 1997 ¹⁷ | Unclear Single initial measurement, no adjustment for time trends, but timeframe within 2 weeks. | Unclear Every 7th enrollee invited, differences between those enrolled and not enrolled in gender and some drug use variables. | Low Timepoints based on initial and follow-up visits. | Unclear Follow-up at 2 weeks, but unclear frequency of SSP use. | Low Structured questionnaires by staff at both timepoints. | Unclear 79% had follow- up data at 2 weeks, but difference in sharing needles between those with and without follow-up. | Low All relevant outcomes appear to be reported. | Unclear |
| Vogt 1998 ¹⁸ | Unclear Single initial measurement, no adjustment for time trends, unclear follow-up. | Unclear Random selection of clients, but unclear how clients were randomly selected and if they differed from those not selected. | Low Timepoints based on initial and follow-up visits. | Unclear Unclear timing of follow-up visits and unclear frequency of SSP use. | Unclear Unclear if structured questionnaire used for interviews. | High Repeat interviews with 51% of participants included for follow-up analysis. Unclear differences between those with and without follow-up. | Low All relevant outcomes appear to be reported. | High |

Abbreviations. GEE=generalized estimating equations; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IDU=injection drug use; SSP=syringe services program.



SYSTEMATIC REVIEWS (ROBIS)

| Study Name or Author Year | Study Eligibility Criteria | Identification and Selection of Studies | Data Collection and Study Appraisal | Synthesis and Findings | Overall Risk of Bias |
|------------------------------|--|---|--|---|----------------------|
| Jones 2010 ² | Low Reasonable and mostly clearly defined eligibility criteria. Do not explicitly describe comparator criteria but specify included study designs. | Low Multiple databases searched. Searches included both key words and controlled vocabulary, but full search syntax is not provided. Date limit of 1990 seems roughly in line with start of research on SSPs, but some studies may have been published prior to this date. Hand-searched reference lists of included studies. No grey literature searching conducted. Dual independent study selection indicated for title/abstract screening but not explicitly stated for full-text review. | Low A single reviewer abstracted data and assessed study quality, checked by another reviewer. Study quality was assessed using appropriate criteria. | Unclear Meta-analysis was not conducted due to variability between studies. Narrative synthesis did not address methodological quality; this is addressed in the discussion section, but individual quality assessments are not included. | Low |
| Palmateer 2022 ¹ | Low Reasonable and clearly defined eligibility criteria. Detailed criteria provided in Appendix. | Low Update to a 2011 review of reviews. Searches included an initial search for systematic review and additional searches for primary studies when indicated. Multiple databases searched. Conducted grey literature searches and hand searched reference lists of included records. Searches included key words and controlled vocabulary terms and full syntax is provided in the Appendix. | Unclear Dual independent study selection, data abstraction, and risk of bias assessment. Risk of bias of systematic reviews was assessed using appropriate criteria. Risk of bias of primary studies was not assessed; instead, study design was considered an indicator of quality. | Low Rated the strength of the evidence for each intervention and outcome using a framework that is clearly described in the review. | Low |

Abbreviations. SSP=syringe services program.



STRENGTH OF EVIDENCE ASSESSMENTS FOR KQ1 PRIMARY STUDIES

| Outcome | Studies | Study Limitations | Directness | Consistency | Precision | Rating and Summary of Evidence |
|--|--|----------------------|------------|--------------|-----------|---|
| Injection frequency | 1 RCT, ³ 6 cohort, ^{4–9} and 9 pre-post ^{10–18} studies | Unclear to high | Direct | Consistent | Precise | Low SSP use does not appear to be associated with an increase in injection frequency. |
| Naloxone distribution | 1 serial cross- sectional ¹⁹ and 4 cross-sectional ²⁰⁻ ²³ studies | High | Indirect | Consistent | Imprecise | Low SSP use may be associated with higher rates of carrying naloxone. |
| Overdose education | 2 cross-sectional studies ^{21,24} | High | Indirect | Consistent | Imprecise | Low SSP use may be associated with receipt of overdose education. |
| Linkage to SUD treatment and utilization of treatment services | 6 cohort ^{4,5,25–28} and 3 pre- post ^{11,16,17} studies | Unclear to high | Direct | Consistent | Precise | Low SSP use may be associated with increased treatment linkage and/or use of treatment services compared to no SSP use (or less use). |
| Syringe disposal | 1 RCT, ²⁹ 2 pre- post, ^{16,17} 11 cross-sectional, ^{30–} ⁴⁰ and 7 ecological ^{41–47} studies | Unclear to high | Direct | Consistent | Imprecise | Low SSP use and/or presence of an SSP does not appear to be associated with an increase unsafe syringe disposal practices. |
| Neighborhood crime rates | 2 ecological studies ^{48,49} | High | Direct | Inconsistent | Imprecise | Low Presence of an SSP does not appear to be associated with an increase in neighborhood crime rates. |



INCLUDED SYSTEMATIC REVIEWS

Citation

Abdul-Quader AS, Feelemyer J, Modi S, et al. Effectiveness of structural-level needle/syringe programs to reduce HCV and HIV infection among people who inject drugs: A systematic review. AIDS and Behavior. 2013;17(9):2878-2892.

Aspinall EJ, Nambiar D, Goldberg DJ, et al. Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis. International journal of epidemiology. 2014;43(1):235-248.

Davis SM, Daily S, Kristjansson AL, et al. Needle exchange programs for the prevention of hepatitis C virus infection in people who inject drugs: a systematic review with meta-analysis. Harm reduction journal. 2017;14(1):25.

European Centre for Disease Prevention and Control. Systematic Review on the Prevention and Control of Blood-Borne Viruses in Prison Settings.; 2018.

Fernandes RM, Cary M, Duarte G, et al. Effectiveness of needle and syringe Programmes in people who inject drugs - An overview of systematic reviews. BMC public health. 2017;17(1):309.

Johnson WD, Rivadeneira N, Adegbite AH, et al. Human Immunodeficiency Virus Prevention for People Who Use Drugs: Overview of Reviews and the ICOS of PICOS. The Journal of infectious diseases. 2020;222(S).

Jones L, Pickering L, Sumnall H, McVeigh J, Bellis MA. Optimal provision of needle and syringe programmes for injecting drug users: A systematic review. The International journal on drug policy. 2010;21(5):335-342.

Lazarus JV, Safreed-Harmon K, Hetherington KL, et al. Health Outcomes for Clients of Needle and Syringe Programs in Prisons. Epidemiologic reviews. 2018;40(1):96-104.

MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: A review of reviews to assess evidence of effectiveness. International Journal of Drug Policy. 2014;25(1):34-52.

Mir MU, Akhtar F, Zhang M, Thomas NJ, Shao H. A Meta-analysis of the Association Between Needle Exchange Programs and HIV Seroconversion Among Injection Drug Users. Cureus. 2018;10(9).

Palmateer N, Hamill V, Bergenstrom A, et al. Interventions to prevent HIV and Hepatitis C among people who inject drugs: Latest evidence of effectiveness from a systematic review (2011 to 2020). The International journal on drug policy. 2022;109:103872.

Palmateer N, Kimber J, Hickman M, Hutchinson S, Rhodes T, Goldberg D. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: A review of reviews. Addiction. 2010;105(5):844-859.

Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. The Cochrane database of systematic reviews. 2017;9.

Puzhko S, Eisenberg MJ, Filion KB, et al. Effectiveness of Interventions for Prevention of Common Infections Among Opioid Users: A Systematic Review of Systematic Reviews. Frontiers in public health. 2022;10:749033.

Sawangjit R, Khan TM, Chaiyakunapruk N. Effectiveness of pharmacy-based needle/syringe exchange programme for people who inject drugs: A systematic review and meta-analysis. Addiction. 2017;112(2):236-247.

Thomson K, Hillier-Brown F, Walton N, Bilaj M, Bambra C, Todd A. The effects of community pharmacy-delivered public health interventions on population health and health inequalities: A review of reviews. Preventive medicine. 2019;124:98-109.

Wright NMJ, Tompkins CNE. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. Harm reduction journal. 2006;3:27.



PEER REVIEW COMMENTS AND RESPONSES

| Comment # | Reviewer # | Comment | Author Response |
|--------------|-----------------|---|--|
| Are the obje | ectives, scope, | and methods for this review clearly described? | |
| 1 | 1 | Yes | None |
| 2 | 2 | Yes | None |
| 3 | 3 | Yes | None |
| 4 | 5 | Yes | None |
| 5 | 6 | Yes | None |
| 6 | 7 | Yes | None |
| 7 | 8 | Yes | None |
| Is there any | indication of b | oias in our synthesis of the evidence? | |
| 8 | 1 | No | None |
| 9 | 2 | No | None |
| 10 | 3 | No | None |
| 11 | 5 | No | None |
| 12 | 6 | No | None |
| 13 | 7 | No | None |
| 14 | 8 | No | None |
| Are there ar | ny published o | r unpublished studies that we may have overlooked? | |
| 15 | 1 | No | |
| 16 | 2 | Yes - Analisa Packham, Syringe exchange programs and harm reduction: New evidence in the wake of the opioid epidemic, Journal of Public Economics, Volume 215, 2022, 104733, ISSN 0047-2727 | Thank you for bringing this study to our attention. It does not meet criteria for inclusion because we did not review evidence from primary studies for HIV incidence or prevalence and drug-related mortality was not one of our pre-specified outcomes. However, this study and the response it inspired from other researchers (Lambdin 2023) is relevant to mention in the discussion section of our review as an example of how misinterpreting |



| Comment # | Reviewer # | Comment | Author Response |
|--------------|---------------|---|---|
| | | | data can lead to unjustified conclusions regarding SSP use and health outcomes. |
| 17 | 3 | No | None |
| 18 | 5 | Yes - https://doi.org/10.1007/BF02351502; https://doi.org/10.1111/jrh.12388 | Thank you for highlighting these citations. The first study (Strathdee 1999) is included in our review and synthesis. The second study (Surratt 2020) is also included but was not prioritized for synthesis because it is cross-sectional and we focused on longitudinal evidence for the outcome of treatment linkages. |
| 19 | 6 | No | None |
| 20 | 7 | No | None |
| 21 | 8 | Yes - Packham A. Syringe exchange programs and harm reduction: New evidence in the wake of the opioid epidemic. J Public Economics 2022; 215. https://doi.org/10.1016/j.jpubeco.2022.104733. Available at https://apackham.github.io/mywebsite/opioidpaper_webcopy.pdf. | Thank you. Please see our response to comment #16. |
| Additional s | uggestions or | comments can be provided below. | |
| 22 | 1 | Table 5: It is not correct that LAAM is no longer approved in the U.S. It is still FDA approved. It was taken off the market voluntarily by the manufacturer because of poor sales. It is the case that it is no longer approved in Europe. | Thank you for making note of this error. We have revised the text to state that LAAM is an opioid agonist no longer on the US market. |
| 23 | 1 | Table 5: Text in the Neufeld row seems incomplete. | Thank you for this comment. Brooner 1998 and Neufeld 2008 are 2 publications associated with a single study and the results are described in a single row. We have edited the study column to improve clarity. |
| 24 | 1 | Table 6: Dasgupta row. What is the "public health response?" | Thank you for this comment. We have added a footnote to specify that the public health response included establishment of the state's first legal SSP. |
| 25 | 1 | Page 25, line 37: Change "along" to "alone." Table 9, Harm Reduction row: Remove either "detox" or "detoxification." | Thank you for making note of these errors. We have made the recommended corrections. |



| Comment # | Reviewer # | Comment | Author Response |
|-----------|------------|---|---|
| 26 | 1 | Page 27, line 35: Change "justice" to "legal." The supposed "justice" system is anything but "just." | Thank you for this recommendation. We have revised the text to state "legal system." |
| 27 | 1 | Page 28, lines 56-57: The trend toward non-injecting of fentanyl may have been short lived. Increasingly, fentanyl is showing up in powder form which is likely to be injected. | Thank you for this comment. We removed the specific reference to fentanyl and instead highlight that drug use patterns are constantly evolving, and future research could help identify best practices for SSPs to respond and maintain relevance. |
| 28 | 2 | Did the ESP review the extant literature for any association between SSP use and substance use? It was included in the SOW we reviewed in late Feb of this year that included the following outcomes: Drug use behaviors (e.g., sharing, borrowing, lending, reuse, or unsafe disposal of syringes; amount, speed, or frequency of use; etc); knowledge of overdose risk; naloxone distribution/use; linkage to treatment for substance use disorder, HIV/HCV, or other medical needs, or to HIV pre-exposure prophylaxis; utilization of referred services. Please note that one recent study (albeit with several methodological flaws) suggests an association between SSP implementation and increases in opioid use: "https://www.sciencedirect.com/science/article/abs/pii/S0047272722001359" Syringe exchange programs and harm reduction: New evidence in the wake of the opioid epidemic - ScienceDirect. However, the author (Analisa Packham) also notes the following: "I note that my findings imply that SEPs do little to reduce drug overdoses and may even exacerbate opioid abuse and misuse. However, the results do not suggest that SEPs are ineffective at curbing addiction for all clients. Moreover, prescription drugs, such as Buprenorphine that reduce symptoms of opiate addiction and withdrawal, or other opiate antagonists, which work in the brain to prevent opiate effects and decreases the desire to take opiate, could be one way for SEPs to mitigate clients' opioid dependence in the future." | Thank you for your comments. The association between SSPs and substance use was partly addressed through our inclusion of injection frequency, but we did not specifically review evidence on whether use of SSPs is associated with more or less frequent drug use overall. This decision reflects the review's focus on the role of SSPs in harm reduction. While we reviewed evidence related to naloxone distribution and overdose education, we did not include drug-related mortality as an outcome of interest. Regarding the Packham 2022 study, please see our response to comment #16. |
| 29 | 2 | [In second bullet of Key Findings, add 's' to 'encourage' and 'facilitate.'] | We have left the wording of the key findings as written, since the phrases regarding naloxone, overdose education, and treatment referral follow "may." |



| Comment # | Reviewer # | Comment | Author Response |
|-----------|------------|---|---|
| 30 | 2 | [Insert citation substantiating first statement of executive summary.] | To be consistent with our usual style, we did not include citations in the executive summary but did include citations related to increased drug use and HIV/HCV in the background section. |
| 31 | 2 | Please define "needs-based" SSP. Are participants required to submit used syringes to get sterile ones? If not, needs-based seems synonymous with the "distribution" model of SSPs. | Thank you for this comment. In the section on SSP models, we have revised the text to use more precise language referring to syringe distribution policies (which may be needsbased or offer a set number of syringes regardless of how many are returned) and exchange policies (which require returning used syringes). |
| 32 | 2 | Are SSPs that use a distribution model (no exchange) considered "more permissive?" | Thank you for this comment. Please see our response to comment #32. We have revised this section to improve clarity regarding the term "permissive." |
| 33 | 3 | One area that is not discussed but may be equally important is acquired bacterial infections from using clean needles when the skin has not been cleansed using an alcohol wipe or other procedure. Cellulitis is prevalent among PWID and can lead to severe adverse outcomes. This reviewer realizes that this may not be within scope, however, due to the newest issue - fentanyl adulterated with xylazine wound issues is becoming a hot topic area. | Thank you for this comment. We agree that bacterial infections related to injection-drug use are an important outcome, but this outcome was not within the scope of this review. In the Future Research section, we added a reference to the emergence of xylazine and importance of studying best practices for SSPs to provide PWID with information and tools to reduce xylazine-specific harms. |
| 34 | 5 | This was a well thought out review recognizing that the research methodology is mixed. The review was concise and appropriately addressed the limitation as well as areas for future research. If I might suggest also adding improving in HIV/HCV treatment as part of linkage to care. For example, a pilot study done in 2003 points to the idea that "health services based on needle exchange may enhance access to HAART among out-of-treatment HIV-infected IDUs" (https://doi.org/10.1093/jurban/jtg053). There's another review that may be helpful, most of the references are already in the current manuscript. however, this article may provide additional references/perspectives (https://doi.org/10.1186/s13722-023- | Thank you for your comments. We included linkage to HIV treatment as an outcome but did not identify any studies that met criteria for inclusion in our synthesis. We did not include studies evaluating HIV or HCV treatment services co-located with SSPs as stand-alone interventions, which the study by Altice 2003 is an example of. We realize that the body of literature on co-located treatment services is of high interest, but reviewing this evidence |



| Comment # | Reviewer # | Comment | Author Response |
|-----------|------------|--|--|
| | | 00394-x). Looks great and thank you for sharing and allowing me to be a part of this! | would have made the scope of this review unfeasibly large. |
| | | | Thank you for providing the link to the scoping review. We hand-searched this publication for relevant references as part of our search process. |
| 35 | 6 | This is my first review of the "Effectiveness of Syringe Service Programs: A Systematic Review". Page numbers reference the page in the PDF document. Generally, the title and corollary mentions of SSPs should be referred to as Syringe Services Programs (missing "s" in services throughout the document; cf. https://www.cdc.gov/ssp/index.html). Not sure if there was any examination of drug test strips (e.g., fentanyl test strips) in this review. Also there is frequent reference to the Office of National Drug Control Policy; however, these efforts also align with other key initiatives related to infectious disease—recommend checking with David Ross and Lorenzo McFarland on the appropriate initiatives to cite (e.g., Ending the HIV Epidemic, etc.). | Thank you for your comments. We have corrected the text to refer to Syringe Services Programs (plural) throughout the document. We did not specifically examine evidence related to drug testing strips. We would have included evidence regarding drug testing strips as a component of harm reduction services provided at SSPs but did not identify such evidence. We specifically highlighted the Office of National Drug Control Policy (ONDCP) because this review was requested in part to inform ONDCP efforts. We added a sentence to the beginning of the Discussion to highlight that harm reduction is a goal of VA Offices of Mental Health and Suicide Prevention, Research and Development, and Specialty |
| 36 | 6 | 1. Page 9, line 10—Key Findings—"carriage" is an uncommon word used | Care Services. Thank you for this suggestion. We have |
| | | regarding naloxone—consider changing to "carrying naloxone" (also on page 10, line 32; page 30, line 50; page 31, line 14; page 40, line 14) | revised the text to state "carrying" or "possession" of naloxone rather than "carriage." |
| 37 | 6 | 2. Page 10—it may be helpful to clarify the difference between "Linkage to SUD treatment and utilization of treatment services" and "Additional harm reduction and referral services" (the latter seems to combine a number of services—e.g., motivation interviewing, case management, pharmacybased SSP referral which seem to be different things). In general, these | Thank you for this comment. We reorganized the findings in this table to improve clarity and removed the row describing "Additional harm reduction and referral services." These findings are best described in the results section where additional context is provided. |



| Comment # | Reviewer # | Comment | Author Response |
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| | | seem like blended concepts. Not sure if it would help to better explain the universe of what is included. | |
| 38 | 6 | 3. Page 15, lines 11-15—suggest using the term "stimulants" to refer to cocaine and psychostimulants (latter is primarily methamphetamine). Even in reference #4, psychostimulants are reported separately from cocaine (see Figure 1, https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7006a4-H.pdf) | Thank you for this suggestion. We have revised the text to use the term "stimulants." |
| 39 | 6 | 4. Page 16, lines 5-9—not sure if you want to use the NASEN reference; https://www.nasen.org/ (over 500 SSPs). | Thank you for this suggestion. We have updated this text to reflect current data from NASEN. |
| 40 | 6 | 5. Page 16, line 16—There is also funding from OMHSP's SUD program to fund harm reduction coordinators (should check with them about that sentence); also the "(PMOP)" should come after Program | Thank you for this comment. Because this paragraph is specific to SSPs funding, we did not expand on other VHA initiatives to promote harm reduction (of which there are many). We have corrected the placement of the PMOP acronym. |
| 41 | 6 | 6. Page 20, line 44—based on the 95% CI that is non-significant right? Not "bordered on non-significant" but actually not statistically significant since it include 1.0 | Thank you for this comment. We have corrected this statement to say "bordered on significance." |
| 42 | 6 | 7. Page 22, line 31—superscript after 5 is underlined and doesn't need to be | Thank you for making note of this error. We have corrected this text. |
| 43 | 6 | 8. Injection Frequency/Table 3—Bartholomew 2021 seems to indicate an increased average # of injections per day. So does Patel 2018. That is 2 of the 16 studies included in this section. Bringing this up in case it needs to be addressed to fend off potential critics. | Thank you for this comment. We added to the section on injection frequency to discuss these 2 studies specifically and provide more context for their findings. |
| 44 | 6 | 9. Page 30, line 14—what is NEP? I don't see it defined anywhere. | Thank you for this comment. NEP refers to "needle exchange program." We have changed this reference to "NEP" to "SSP" instead to be consistent with the language of our review. |
| 45 | 6 | 10. Page 32, lines 11-12—The confidence interval includes 1.0, is this not statistically significant? (same as Page 33, line 11) | Thank you for this comment. You are correct that this finding was not statistically significant. We have revised the text to include that point. |
| 46 | 6 | 11. Page 32, line 30—square typo | Thank you for making note of this error. We have corrected this text. |



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| 47 | 6 | 12. Page 32, line 49-50—this is not statistically significant right? | Thank you for this comment. You are correct that this finding was not statistically significant. In most cases, we do not comment on statistical significance in the table (regardless of whether a given finding was significant or non-significant) for the sake of brevity. |
| 48 | 6 | 13. Page 32, line 55—this is not statistically significant right? | Please see the response to comment # 47. |
| 49 | 6 | 14. Page 33, line 21—IVDU=Intravenous Drug Use right? | Thank you for making note of this error. We have corrected this text. |
| 50 | 6 | 15. Page 34, line 5—this is not statistically significant right? | Please see the response to comment # 47. |
| 51 | 6 | 16. Page 35, lines 6-7—is there an extra number in the 2nd set of parentheses? | Thank you for this comment. We have added a footnote to specify that counts were made at 2 time points pre-SSP and 3 time points post-SSP. |
| 52 | 6 | 17. Page 36 line 37—think "along" should be "alone"; should probably be a comma after "meta-analysis" as well | Thank you for making note of these errors. We have corrected the text. |
| 53 | 7 | Comments to the author: This is a timely and important systematic review of the association of syringe service programs and relevant outcomes such as HIV and HCV prevalence and incidence. This report has a potential for high impact by encouraging the implementation of syringe service programs in the VA. There are several strengths to this review which include clear writing, rigorous and thorough methods, use of person-first language, and including a comprehensive group of outcomes. | Thank you for this comment. |
| 54 | 7 | Minor comments: 1. The statements from public health organization and professional society regarding syringe service programs are greatly appreciated. The authors may also consider adding statements from the American Academy of Addiction Psychiatry (AAAP) and American Society of Addiction Medicine (ASAM). | Thank you for this suggestion. We have added a policy statement from AAAP but could not locate a current statement from ASAM. |
| 55 | 7 | 2. Including a description of the cost-benefits of implementing syringe service programs may strengthen the discussion, given the relatively low cost of syringes. | Thank you for this suggestion. We revised the Discussion text to specifically highlight the CDC's statements regarding SSPs as "cost-saving." |



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| 56 | 8 | p. 9 (pdf p. 20) – Re: Reference 24 Palmateer et al. Int J Drug Policy. 2022;109:103872. Regarding conclusion that pooled studies did not show an effect on HCV transmission, please consider commenting on whether: Studies were appropriate for pooling, e.g., similar populations, interventions, and outcomes. pooled studies had adequate power to detect a difference in HCV transmission. ascertainment bias may have been present, e.g., low HCV testing rates in SSP utilizers | Thank you for your comments. We did not directly assess the quality of evidence for this outcome because we relied on the evidence synthesis conducted by the Palmateer et al. review of reviews, which we assessed to have a low overall risk of bias based on the ROBIS tool. The Palmateer et al. review in turn primarily relied on a Cochrane review and meta-analysis (Platt et al.). While we are unable to address your comments in detail, we have no reason to suspect that the conclusions reached by Palmateer et al. and Platt et al. were inappropriate. |
| 57 | 8 | 2. p. 11 (pdf p. 22) – Primary studies Please consider comment on the following: a. Adequacy of statistical methods. Did studies have: Pre-specified hypotheses? Pre-specified statistical analysis plan? Appropriate adjustments for multiple comparisons? b. Confounders. Did studies address or have data on: population shifts in or out of the SSP's catchment? Other factors which may have affected outcomes, e.g., public health campaigns on HIV testing, promotion of SSPs in community? Length of time over which the study measured outcomes? c. Outcomes. Did any studies examine: HIV or HCV testing rates Deaths or hospitalizations due to overdoses? | Thank you for your comments. Duration of follow-up for primary studies is reported in Table 2. Statistical methods and potential risk of bias due to confounding were evaluated as part of the quality assessment of primary studies (details are located in the Appendix). HIV/HCV testing rates and overdose hospitalizations and deaths were not within the scope of this review. |

