NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

Supervised Injection Facilities and Other Supervised Consumption Sites: Effectiveness and Value

Research Protocol

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1. Background, Objectives, and Research Questions

1.1 Background

Substance use, including the public health crisis in the United States (US) known as the opioid epidemic, is an increasingly common public health concern. In 2018 there were 46,802 opioid overdose fatalities in the US or about 130 Americans dying every day from such overdoses.[1] Drugs may be consumed by various routes, but injection drug use generally has the highest risk of fatal overdose.[2,3] Overall life expectancy in the US began to decrease in 2015, largely driven by the opioid epidemic,[4] and this trend continued through 2016, the first such decrease since the 1960s.[5] On October 27, 2017, the Acting Secretary of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[6] The Council of Economic Advisers estimates the overall economic cost of the opioid crisis to society to be $504 billion, or 2.8% of US gross domestic product.[7]

Injection drug use (IDU) has individual risks beyond overdose. Sharing of the equipment and drugs used for injection can result in transmission of infections such as HIV and hepatitis C.[8] The use of contaminated equipment also increases the likelihood of bacterial infections including local abscesses, suppurative thrombophlebitis, bacterial endocarditis, and bacterial sepsis.[9,10]

Drug use also has broad community impacts. The distribution and sale of drugs can be associated with violence, theft, and hazardous litter.[11] Public intoxication and the visible use of drugs in public spaces can affect all aspects of commercial and non-commercial life in a community.[12,13]

Harm reduction refers to actions and policies intended to reduce the negative consequences of a behavior.[14] Attempts at harm reduction for people who inject drugs (PWID) in the US has focused mainly on syringe services programs (SSPs) that provide clean needles and syringes either as exchanges for contaminated products or freely to PWID providing a multi-day or multi-week supply.[15] Some version of these programs exist in most states.

Supervised (or "safe") injection facilities (SIFs) are another form of harm reduction, but are not yet available in the US.[10] SIFs provide a site where clients may go to inject drugs and where medical personnel are present with the ability to provide naloxone, an antidote for opioid overdose, and other first-responder care.[16,17] In addition, SIFs support risk reduction strategies (e.g., infection prevention) and offer a link to social and medical services.[18,19] SIFs exist more widely in Europe and have been studied in multiple locations for their effects on reducing overdose death and their effects on communities.[18,20] In the US, some cities and states are exploring the feasibility and expected outcomes of opening SIFs to address the individual and public impacts of IDU.[10,18,21]

1.2 Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of SIFs. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). The model analysis plan will provide details on the proposed methodology and model structure that will be used for the economic evaluation (expected publication August 11, 2020).

1.3 Research Questions

To inform our review of the clinical evidence, we have developed the following research question with input from researchers, clinicians, and other public health experts:

- What is the net health benefit of implementing a SIF versus no SIF in the population(s) described below?

1.4 PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting, and Study Design) elements.

Population

The population of focus for the review is all PWID. In an expanded analysis, we will also consider people who use drugs (PWUD) via different forms of consumption (e.g., smoking), as a person-centered approach to this intervention considers harm reduction for the individual, not the type of drug consumption.

We will also seek evidence on subpopulations suggested by the stakeholders, looking for evidence of subgroup effects:

- Housing status, comparing effects in people living with homelessness or unstable housing and those with stable housing

- Injected drug class, comparing effects in people who inject opioids with effects in people who inject stimulants such as cocaine or methamphetamine

Although the population will be PWID or PWUD, the unit of analysis may be cities, or neighborhoods within cities, that implement or do not implement SIFs.

Interventions

The intervention of interest will be the implementation of SIFs including sites that permit other forms of drug consumption.

Comparators

Data permitting, we intend to compare SIFs to not having a SIF and to SSPs. We recognize a variety of SIF intervention models exist and will explore the possibility of comparing them in terms of outcomes of interest.

Outcomes

The outcomes of interest are described in the list below.

- Individual outcomes
    - Overdose
        - Requiring EMS/ambulance or hospital care
        - Mortality (occurring in or out of the facility)
    - All-cause mortality
    - Infection
        - Chronic viral infection (Hepatitis C and HIV)
        - Bacterial infection requiring hospitalization (e.g., antibiotics, surgery)
        - Skin and soft tissue infection not requiring hospitalization
    - Health-related quality of life
    - Intermediate outcomes
        - Use of treatment and recovery support services
        - Receipt of social (e.g., housing), primary medical care, dental and mental health services
        - Injection behaviors (e.g., needle sharing)
    - Drug consumption (e.g., frequency, amount)
- Community and environmental outcomes
    - Syringe and paraphernalia disposal
    - Public drug use
    - Drug-related crime

    - Drug use prevalence
- Health system utilization
    - Hospitalizations
    - Emergency department visits
    - EMT/paramedic calls/responses

Timing

Evidence on intervention effectiveness and safety will be collected from studies of any duration.

Setting

The setting of interest will be community SIFs, whether they are affiliated with health centers and hospitals, and mobile SIFs, or not. Inpatient SIFs are not part of the scope of this review.

Study design

We will seek evidence from randomized controlled trials, non-randomized controlled trials, and observational studies of any duration and sample size.

2. Evidence Review Methods

2.1 Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on the implementation of SIFs will follow best-established methods.[22,23] The review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, PsycINFO, and Web of Science database to identify relevant studies of SIFs. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 2.1 – 2.3 below. We will also search for systematic reviews of SSPs in MEDLINE and PsycINFO. The proposed search strategy is presented in Table 2.4.

To supplement the database searches, we will perform a manual check of the reference lists of included articles, SIF evaluation reports, and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, evaluation documents, any information submitted by stakeholders, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Table 2.1. Search Strategy for SIFs: Medline 1996 to Present with Daily Update and PsycINFO

1	((supervised or safe* or drug) adj2 (inject* or shooting or consumption or smok* or inhal*) adj3 (facilit* or room* or galler* or cent* or site* or service*)).ti,ab.
2	(overdose adj3 prevention adj3 (site* or service*)).ti,ab.
3	1 or 2
4	(addresses or autobiography or bibliography or biography or clinical trial, phase i or comment or congresses or consensus development conference or dictionary or directory or duplicate publication or editorial or encyclopedia or guideline or interactive tutorial or newspaper or commentaries).pt.
5	3 not 4
6	(animals not (humans and animals)).sh.
7	5 not 6
8	limit 7 to English language
9	remove duplicates from 8

Table 2.2. Search Strategy for SIFs: EMBASE

#1	((supervised OR safe* OR drug) NEAR/2 (inject* OR shooting OR consumption OR smok* OR inhal*) NEAR/3 (facilit* OR room* OR galler* OR cent* OR site* OR service*)):ti,ab
#2	(overdose NEAR/3 prevention NEAR/3 (site* OR service*)):ti,ab
#3	#1 OR #2
#4	#3 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)
#5	#4 NOT [medline]/lim
#6	#5 AND [english]/lim

Table 2.3. Search Strategy for SIFs: Web of Science -to Present

#1	TS= ((“supervised” OR “safe*” OR “drug”) NEAR/2 (“smok*” OR “inhal*” OR “inject*” OR “consumption” OR “shoot*”) NEAR/2 (“facilit*” OR “service*” OR “room*” OR “galler*” OR “cent*” OR “site*”))
#2	TS= “overdose prevention sites” OR TS=“overdose prevention service*”
#3	#1 OR #2
#4	#3 Refined by: [excluding] Databases: (MEDLINE)

Table 2.4. Search Strategy for SSPs: Medline 1996 to Present with Daily Update and PsycINFO

1	Needle-Exchange Programs/
2	((needle* or syringe* or inject*) adj3 (program* or service* or exchange* or distribut* or dispens*)).ti,ab.
3	1 or 2
4	(systematic review or meta-analysis).pt.
5	((systematic* adj2 review*) or meta-analys* or ((evidence or quantitative) adj2 synthes*)).ti,ab.
6	4 or 5
7	3 and 6
8	(animals not (humans and animals)).sh.
9	7 not 8
10	limit 9 to english language
11	remove duplicates from 10

2.2 Eligibility Criteria

Studies that do not meet the PICOTS criteria defined above will be excluded. Further, studies will be excluded if they are presenting overlapping results in separate articles.

2.3 Selection of Eligible Studies

Following the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using Distiller SR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

2.4 Data Extraction Strategy

Data will be extracted into the evidence table. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of study populations, location of study, sample size, duration of follow-up, study design features, interventions, outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.

2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

2.5 Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials, using the categories "good," "fair," or "poor." [25]

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered, and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

Further, we will use 12-item National Heart Lung and Blood Institute (NHLBI) Quality Assessment Tool to assess the quality of the pre-post studies with no control group and 14- item NHBLI Quality Assessment Tool for observational cohort and cross-sectional studies, using the categories as "good," "fair," or "poor" quality.[26]

Good: *A study has the least risk of bias, and results are valid*.

Fair: *A study susceptible to some bias deemed not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses*.

Poor: *A study that has a significant risk of bias. Studies rated poor are excluded from the body of evidence.*

2.6 Publication Bias Assessment

Given the emerging nature of the evidence base for this intervention, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. We will select studies that would have met our inclusion criteria, and for which no findings have been published. We will also seek input from experts to potentially identify any unpublished evidence and provide a qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of the study results in the published literature.

2.7 Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base, (2) synthesis of outcome results, and (3) heterogeneity and subgroups.

Summary of Evidence Base

The studies will be summarized in the text and evidence tables of the Evidence Report. This summary is key to understanding the evidence base on the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, population characteristics, interventions (including location), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for the intervention on each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

Analyses are expected to be descriptive only, as differences in entry criteria, study populations, outcome assessments, and other factors are likely to preclude formal quantitative direct or indirect assessments of SIFs versus no SIFs and SSPs. Nevertheless, if studies are sufficiently similar in terms of study populations, outcomes assessed, interventions, and comparators, we will conduct random effect pairwise meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes

results from multiple studies that assessed the same intervention and comparator.[27] The specific approach for any meta-analysis will depend on the available evidence and will be detailed in the report.

Heterogeneity and Subgroups

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, if the studies differ concerning the characteristics including but not limited to, study population, duration of follow-up, study design differences, route of drug consumption, or outcome assessment; these differences will be highlighted in the discussion of the evidence.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2010. [24] Additional explanation of each item can be found in Liberati et al. 2009. [28]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication	Study Design	Intervention (n)	Inclusion & Exclusion Criteria	Population Characteristics	Outcomes