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Scientific Background

The United States (US) continues to face decades-long increases in opioid overdose mortality [1]. The Centers for Disease Control and Prevention (CDC) estimates nearly 775,000 people have died of an opioid overdose since 1999 [2]. Between 2020 and 2021, overdose mortality rates involving heroin and synthetic opioids, other than methadone, increased 22%. Overall, drug overdose deaths in the US increased for all genders; all age groups over the age of 25; American Indian/Alaskan Native, non-Hispanic White, non-Hispanic Black, Hispanic, and Native Hawaiian/Pacific Islander communities; all census regions; and urban, suburban, and rural settings [3].

Opioid overdoses involve a toxic dose of natural opioids like heroin, semi-synthetic opioids like oxycodone, and/or synthetic opioids like fentanyl. Naloxone, an opioid antagonist, is an evidence-based biomedical intervention that effectively reverses opioid overdose when administered intranasally or intramuscularly [4-7]. Opioid antagonists bind to the brain's opioid receptor sites, which displaces any opioid currently in the system and temporarily negates their effects, saving the individual's life. Use of naloxone does not cause dependence or tolerance, and can, though not always, precipitate withdrawal [5-8]. Naloxone can dramatically reduce opioid overdose mortality when distributed to people likely to experience or witness an opioid overdose and packaged with education on its use, known as overdose education and naloxone distribution (OEND)[9-14].

Syringe services programs (SSPs) have a primary function of distributing safe drug use supplies, such as sterile syringes, pipes, injection-related equipment, wound care materials, etc., to facilitate the reduction of harms associated with drug use for their participants. Often, SSPs are the first to hear from their participants regarding changes in the unregulated drug market, drug use trends, and overdose experiences. Most SSPs provide a variety of other evidence-based interventions to improve the health of people who use drugs, including OEND [15-18]. SSPs reach people at high risk for experiencing or witnessing an opioid overdose, and pioneered the development of OEND [19-21]. With staff who are culturally competent in providing services for people who use opioids and pre-existing delivery systems designed to reach participants in their own environment, SSPs are an ideal venue for OEND.

Research documenting OEND's effectiveness (i.e., intervention effectiveness) for reducing opioid overdose mortality emerged over 15 years ago [7]. Only recently have studies begun to assess elements of OEND implementation effectiveness within SSPs [22-26]. As an organizational-level construct, implementation effectiveness can be defined as the aggregated consistency and quality of intervention use within an organization [27]. Findings from recent research identify factors from both the external and internal context of SSPs that shape effective implementation of OEND [22-26]. Yet, to date, no studies have assessed whether implementation strategies (i.e., approaches to improve the adoption, implementation, or sustainment of evidence-based practices) can advance implementation effectiveness of OEND within SSPs.

External facilitation-based implementation strategies have been identified as a promising approach to advance implementation outcomes [28-39]. Fundamentally, these approaches involve a person external to the organization providing interactive problem solving and support to assist implementation efforts. Often, their work is in conjunction with other implementation strategies. Whether such an approach can help SSPs, which often face substantial community, financial, and legal constraints [40], effectively implement OEND remains an important area of inquiry.

Study Objective

As such, we conducted a randomized controlled trial of 105 SSPs throughout the US to understand the effectiveness of a multifaceted, external facilitation-based implementation strategy at advancing OEND implementation effectiveness within SSPs.

Scientific Methods

Trial Design

We conducted a randomized controlled trial of SSPs throughout the US and US Territories. SSPs were assigned to one of two implementation conditions using simple randomization. A standardized checklist aided this paper's clarity and transparency for describing an intervention and reporting a randomized controlled trial [41, 42]. RTI International's Institutional Review Board (IRB) approved and provided oversight for all research activities (STUDY00020448). This trial was registered at ClinicalTrials.gov as NCT03924505.

Study Setting

The target population was operators of SSPs located throughout the US and US Territories. Prior to launching the trial, 342 SSPs were known to be operating in the US and US Territories. Described elsewhere [25], our team launched a national survey of syringe services programs (NSSSP) in February 2019 of all known SSPs operating throughout the US and its Territories, receiving a response from 263 (77%) SSPs. NSSSP responding SSPs were located in the Northeast (13%), Midwest (21%), South (24%) and West (42%) census regions. Among the responding SSPs, 247 (94%) were implementing OEND for their participants [25].

Recruitment, Eligibility, and Enrollment

To be eligible, an organization must have: 1) met the definition of an SSP – a program which primary function is to engage people who use drugs and provide them free drug use supplies to reduce harms associated with drug use, 2) implemented OEND for a minimum of 6 months, and 3) completed the NSSSP fielded from February to July 2019. We excluded organizations such as fire departments or emergency departments of hospitals that offered drug use supply distribution since it would be an ancillary function of these organizations and OEND programs that were not part of a SSP.

A total of 243 SSPs participated in the survey and were determined to be eligible. SSPs were organized into a randomized list and were contacted sequentially for recruitment into the trial. We recruited SSPs from September 2019 to February 2021. Within that timeframe, we paused recruitment activities from March to July 2020 due to the onset of the COVID-19 pandemic. The pause in recruitment activities primarily provided an opportunity for SSPs to adapt to COVID-19 changes, particularly for their adjustment to stay-at-home orders and adoption of delivery models that minimized close person-to-person contact.

To recruit SSPs, our study team initially contacted people in leadership role(s) at each SSP via email to set up a call to explain the study and carry out enrollment activities for organizations that were interested. Organizational leadership included executive directors, program managers, and/or site coordinators. For organizations interested in participating in the trial, study staff would obtain electronic/written informed consent from the organization to join the study, carry out the organizational agreement for participation, and administer the baseline survey. Following the baseline survey, SSPs were randomized using simple randomization to two study arms: 1) dissemination of OEND best practice recommendations (i.e., Control SSPs), or 2) the Organize and Mobilize for Implementation Effectiveness (OMIE) approach along with dissemination of the OEND best practice recommendations (i.e., OMIE SSPs). Sequentially numbered sealed envelopes were used to implement the random allocation sequence, which were concealed until the point of randomization.

OEND Best Practice Recommendations

Study staff disseminated best practice recommendations to all SSPs enrolled in the trial. Details of OEND best practice recommendations can be found elsewhere [43]. Briefly, a Delphi study was carried out to develop a set of best practices for OEND implementation within SSPs. Experts for the Delphi study included people in paid and volunteer leadership and direct service positions in SSPs, OEND researchers, people who work in state or local health departments, and people who use drugs who deliver and access SSP/OEND services. All individuals had prior or current experience delivering OEND programming in community-based settings, and people with lived and living substance use experience were represented in each of the expert categories. Findings from this initiative were summarized into a best practices implementation guide (Appendix A).

Organize and Mobilize for Implementation Effectiveness (OMIE)

Table 1 defines and specifies the 8 discrete implementation strategies that comprised OMIE. The OMIE approach was based on the Implementation and Sustainment Facilitation (ISF) Strategy, which is grounded in the theory of implementation effectiveness [27], and added discrete strategies from the Addiction Technology Transfer Center (ATTC), which were considered necessary elements from the original trial. Both ISF and ATTC have been described extensively elsewhere [44, 45]. Overall, our multi-component approach used external facilitation as the overarching strategy, by which seven other strategies were leveraged to support SSP staff and leadership. In total, 4 out of 7 discrete strategies from ISF were combined with 4 out of 10 discrete strategies from ATTC, detailed in Table 1. In addition to external facilitation, our multi-faceted OMIE approach included: organize implementation team meetings, identify and prepare champions, develop and organize quality monitoring system, assess for readiness and identify barriers, distribute educational materials and resources, conduct educational meetings, and provide ongoing consultation. The study team, comprised of people who had delivered SSP-based OEND services in the past year, researchers with over 20 years of SSP and OEND research experience, and national OEND implementation experts, collaboratively decided upon the discrete strategies for the OMIE approach. Decisions were grounded in shared understanding and discussion of implementation barriers SSPs faced generally and with OEND specifically.

Table 1. Specification of Organize and Mobilize for Implementation Effectiveness

Discrete strategy	Definition, actor, action, action target and temporality specification
1. External Facilitation	Definition: provision of guidance, resources and coaching from an implementation expert who is external to the organization. Actor: individual with previous OEND implementation experience within SSP settings. Action: overarching mechanism by which the below strategies were delivered to SSP staff. Action Target: SSP staff, including naloxone implementation team and leadership. Temporality: Begins within 1 month of enrolling into the trial, occurs up to monthly for twelve months.
2. Organize implementation team meetings	Definition: develop and support implementation team who are implementing OEND, giving them protected time to focus on implementation efforts, share experiences and support one another. Actor: external implementation advisor (see above). Action: web-based meetings with direct interaction between external implementation advisor and SSP staff. Action Target: SSP staff, including naloxone implementation team and leadership.

	Temporality: Begins within 1 month of enrolling into the trial, occurs up to monthly for twelve months.
3. Identify and prepare champions	Definition: cultivate relationships with people who will champion and generate excitement within the organization regarding OEND best practice implementation. Actor: external implementation advisor (see above). Action: focused relationship building with SSP staff who are OEND implementation champion(s). Action Target: SSP staff, including OEND implementation team and leadership. Temporality: Begins with first organizational team meeting and continues as needed for 12 months
4. Develop and organize quality monitoring system	Definition: develop and introduce an electronic tool that can be used to assess and prioritize best practice implementation efforts. Actor: external implementation advisor (see above). Action: using the electronic tool, external implementation advisor works with SSP staff to assess OEND best practice implementation and prioritize areas for focused efforts. Action Target: SSP staff, including OEND implementation team and leadership. Temporality: begins with first organizational team meeting and continues up to monthly for 12 months
5. Assess for readiness and identify barriers	Definition: assess SSPs to determine degree of readiness for best practice implementation, and barriers that may impede implementation. Actor: external implementation advisor (see above). Action: focused conversation to discuss activities required for best practice implementation, readiness to carry out those activities and potential barriers that could impede those efforts. Action Target: SSP staff, including OEND implementation team and leadership Temporality: begins within 1 month of enrolling into the trial, occurs up to monthly for twelve months
6. Distribute educational materials and resources	Definition: distribute educational materials (manuals, online trainings, etc.) electronically with regards to OEND best practices Actor: external implementation advisor (see above). Action: electronically distribute OEND best practices manual and other resources including implementation manuals and online trainings Action Target: SSP staff, including OEND implementation team and leadership Temporality: begins with first organizational team meeting and continues as needed for 12 months
7. Conduct educational meetings	Definition: conduct educational sessions for providers and leadership with regards to OEND best practices Actor: external implementation advisor (see above). Action: web-based trainings with direct interaction between external implementation advisor and SSP staff. Action Target: SSP staff, including OEND implementation team and leadership Temporality: begins with first organizational team meeting and continues as needed for 12 months.
8. Provide ongoing consultation	Definition: provide implementers with continued consultation with with regards to OEND best practices. Actor: external implementation advisor (see above). Action: web-based meetings with direct interaction between external implementation advisor and SSP staff. Action Target: SSP staff, including OEND implementation team and leadership Temporality: begins within 1 month of enrolling into the trial, occurs via web-based meetings up to monthly for twelve months and as needed via electronic communication

SSP staff and organizational leadership in the OMIE arm were provided the opportunity to participate in 60-minute sessions once a month for up to 12 months. In addition to monthly sessions, facilitators were provided up to 2 hours to prepare for sessions and to identify and distribute resources to SSPs based on identified priorities. All sessions were offered virtually over audio-visual connections. Thus, the maximum possible dose for each SSP was 12 sessions or 36 hours. To maximize the extent to which the approach was implemented with consistency and quality, the project's lead and the study coordinator trained each facilitator, reviewed randomly selected facilitation session recordings, and held group supervisory meetings weekly to discuss successes, lessons learned, and emerging issues.

Data Collection

We carried out an interview-administered survey at SSPs baseline visit and at their 12-month follow-up after all facilitation-based activities had occurred. SSPs were paid a $50 incentive for their time (~30 minutes) completing the baseline and the 12-month follow-up survey. In addition, the study coordinator tracked the number of sessions and the number of hours between external facilitators and SSP teams as part of a log of implementation activities. Follow-up to complete the 12-month follow-up survey ended in February 2022, marking the end of the trial approximately 12 months after the last SSP was enrolled.

Trial Outcomes

Our primary outcomes center on the multidimensional variable of implementation effectiveness (i.e., the consistency and quality of OEND implementation by SSP staff). Implementation effectiveness fit our broad objectives, by focusing on the extent to which our multifaceted, facilitation-based approach impacted OEND delivery at the organizational level. Accordingly, SSPs represent the primary unit of analysis. Proctor et al.'s taxonomy of implementation outcomes informs our operationalization of implementation effectiveness, focusing on the reach of SSPs' naloxone distribution (i.e., consistency) and fidelity to OEND best practices (i.e., quality)[46]. As such, the primary outcomes were the number of naloxone doses distributed in the past 3 months; the number of SSP participants receiving naloxone in the past 3 months, and the number of OEND best practices implemented. Importantly, prior research has shown that larger scale naloxone distribution has led to reductions in opioid overdose mortality, further supporting use of these measures as trial outcomes [17, 47, 48].

Covariates

The baseline survey also collected information on region of operation, the number of staff and volunteers at the SSP, staff training in OEND, the prior year's annual budget in dollars, the number of participant contacts at the SSP in the past 3 months.

Masking

Masking the SSP organizations and their staff to the assigned implementation strategy condition was not possible. Aside from the external facilitators who delivered the implementation strategies, research staff were blinded to all condition assignments, including the statistician throughout all analyses.

Targeted Sample Size

The targeted sample size was estimated using PASS software [49]. We estimated that a sample of 100 SSPs (50 per arm) would provide 80% statistical power to detect a statistically significant ($p<0.05$) medium effect size (Cohen's $d = 0.45$)[50] between study arms, assuming an

alpha of 0.05, standard deviation of 1.0 and two repeated measurements (baseline and 12-month follow-up) with a first-order autoregressive covariance structure and a correlation between observations on the same SSP of 0.3.

Statistical Analysis Plan

Statistical analyses were conducted using an intent-to-treat approach. Descriptive statistics were used to summarize continuous outcomes and covariates by experimental condition; frequencies and percentages were used to summarize categorical measures. Given the varying sizes of SSPs, counts of naloxone doses and individuals receiving naloxone were summarized as a rate per number of participant contacts for syringe services in the past 3 months.

Negative binomial regression models were used to compare the number of naloxone doses distributed and contacts for naloxone refills or trainings by condition; the number of contacts for syringe services in the past 3 months was included as an offset. The model for naloxone doses was adjusted for baseline rate given the difference between conditions at baseline. The mean number of best practices adopted were compared by condition using a two-sample t-test. We also carried out a per-protocol dose response analyses, where OMIE SSPs were dichotomized at the median for the number of OMIE sessions (<10 sessions; 10+ sessions) and number of OMIE hours received (<12 hours; 12+ hours) and compared to Control SSPs. P-values <0.05 were considered statistically significant a priori. All analyses were conducted using Stata 16.1 (StataCorp LLC, Texas USA).