Clinicaltrials.gov Registration #: NCT04253782

Protocol Title: *A Multi-Tiered Safety Net Following Naloxone Resuscitation from Opioid Overdose*

Version Date: 05/26/2021

Study Protocol and Statistical Analysis Plan

HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: *A Multi-Tiered Safety Net Following Naloxone Resuscitation from Opioid Overdose*

Principal Investigator: Daniel Joseph, MD

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INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. Statement of Purpose: State the scientific aim(s) of the study, or the hypotheses to be tested.

Our principal aim is to determine whether a novel biopsychosocial intervention following opioid overdose (OD) affects 1) the frequency of secondary opioid OD events and 2) the proportion of individuals who remain engaged in treatment for opioid use disorder (OUD) or are in remission at 30 days and at 180 days post consent. We define remission as engagement in daily medication-assisted therapy (MAT)—typically buprenorphine/naloxone (BUP) or methadone— and/or a recovery capital score of ≥ 27.5.[1] Our intervention will connect individuals with important community resources that hopefully will facilitate progress toward long-term recovery. Specifically, we will link individuals with moderate-severe OUD, who have experienced at least 1 opioid OD requiring naloxone resuscitation but refused BUP treatment, if offered, with 1) treatment with BUP, 2) methadone maintenance, intensive outpatient, or residential treatments, or 3) education materials from the Connecticut Community for Addiction Recovery (CCAR). Enrolled participants may switch from 1)-3) throughout. To carry out the intervention, an addiction **r**ecovery **c**oach from CCAR and a health educator (research) **p**aramedic will form a team (RCP team) and perform remote (including over-the-phone) and/or electronic follow-up visits after a participant has experienced at least 1 opioid OD requiring naloxone resuscitation. Our hypothesis is that the intervention, by the RCP team, connecting participants to community resources will decrease subsequent OD events and increase the likelihood of remission. To evaluate this hypothesis, data will be collected from self-report and from EPIC, Yale New Haven Hospital's (YNHH) medical record system. If the sources of information appear to conflict, then what is entered in EPIC will take precedence.

Our secondary aim is to determine whether the intervention affects 1) the frequency of positive-urine tests for opioids and 2) the frequency and proportion of subjects self-reporting opioid use. (We recognize that, due to constraints on in-person follow-up imposed by the COVID-19 pandemic, individuals who are most likely to get urine tests are those who are in treatment and those who might subsequently present to the emergency department (ED) for opioid-related complaints.) Our hypothesis is that our intervention will decrease both. As in the previous aim, data will be collected remotely/electronically from self-report and EPIC. If the sources of information were to conflict, then what is entered in EPIC will take precedence.

Data from our entire cohort will be compared in aggregate with patients who were started on BUP in the ED over the same time period and with historic controls who received only printed resources addressing OUD as reported in D'Onofrio et al.[11]

2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.

The probable duration of the project is 2 years (from 09/2019-09/2021). There is potential for extension after this time, depending on availability of funding.

3. Background: Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Importance of problem.

The epidemic of opioid use disorder (OUD) prompted a presidential declaration of a public health emergency in October, 2017, and it was extended in January, 2018.[2] In 2016, an unprecedented 63,632 deaths in the United States (US) were attributed to drug overdose; 2/3 of these involved opioids.[3] The deaths due to drug overdose in 2016[4] exceeded the number of traffic fatalities during the peak year of 1972,[5] the number of HIV deaths at their peak in 1995, the final year before the introduction of triple antiviral therapy,[6] and the peak year for gun violence in the US, which was 1993.[7,8] Nonfatal opioid overdoses are highly associated with ongoing OUD and recurrent overdoses. One study reviewing emergency medical service (EMS) records of

164 persons with fatal opioid overdose found that 62% had been treated for at least one previous overdose, while 17% had 3 or more prior overdoses.[9] In another large study involving a single health system, nearly 10% of patients presenting with nonfatal drug overdoses were deceased within 12 months, though not all deaths were due to fatal overdoses.[10] Their findings in that study reflect some of the changing demographics of OUD, as multi-variate analysis showed increased age, comorbidities such as cancer and end-stage renal disease, and polypharmacy correlated with the highest 1-year mortality.

Scientific premise for proposed project.

Buprenorphine/naloxone-based (BUP) treatment for OUD.

It is known that MAT of OUD with BUP is associated with decreased risk of opioid overdose, improved engagement in treatment at 30 days, and less self-reported opioid use compared with those who receive only a brief negotiated interview (BNI) or referral for counselling.[11,12] As a result of this previous research at our institutions, patients in our ED who are successfully resuscitated with naloxone following an opioid overdose are routinely screened using the Mini International Neuropsychiatric Interview (MINI) [13,14] for OUD. Those who screen positive for moderate to severe OUD are offered initiation of BUP treatment in the ED, with outpatient primary care clinic referral for ongoing medical monitoring and treatment. At the time of the ED visit, however, fewer than half of these patients will consent to initiation of BUP.[15] Those who decline are offered overdose education and naloxone (OEN) by ED staff. A safety net that includes tailored linkage plans to effectively engage opioid overdose survivors with BUP, intensive psychosocial support, and follow-up counseling in the community is needed. To gain a better understanding of the motivations of those who decline the offer of BUP, we have purposively sampled 16 opioid overdose survivors who agreed to participate in a qualitative research study looking at their knowledge and understanding of OUD (unpublished). Predominant themes included the following: ambivalence regarding the effectiveness of treatment for OUD, concerns about concurrent social supports such as housing and mental health services; lack of appreciation for the risks associated with OUD (even with multiple prior overdoses); strong, but abstract desire to discontinue use of opioids, despite refusal of treatment; and limited understanding of how to prevent or emergently manage overdoses. These perceptions from the patient population with OUD declining treatment directly informed our proposed research strategy, which connects affected participants with community resources such as treatment with BUP.

Peer support and recovery in OUD.

In 2012, the Substance Abuse and Mental Health Services Administration (SAMHSA) established a working definition of recovery from mental health and substance use disorders: a process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential.[16] The definition identifies 4 dimensions that support recovery: 1) health, including both management of the disease and decision making associated with physical and emotional wellbeing; 2) home, e.g., a stable place to live; 3) purpose, e.g., meaningful daily activities; and 4) community, e.g., supportive relationships and social networks. One of the interrelated guiding principles of recovery promulgated by SAMHSA is peer support. Peer recovery support services are delivered by persons who have common life experiences with those they are serving.[17] Since 1998, SAMHSA has sponsored Recovery Community Services grant programs, and in 2002 the program changed its focus to emphasize the use of peers for recovery support services.[18] This funding now targets recovery community statewide networks. The Connecticut Community for Addiction Recovery (CCAR) was established in 1998, with initial funding by the State's Department of Mental Health and Addiction Services and one of the original SAMHSA grants. Since then, it has grown to its current size with a staff of 28 recovery centers located in major cities, an ED recovery coach program, and 308 volunteers who donated 28,841 hours in 2017 alone. CCAR recovery coaches are peer experts; many have been in recovery themselves. They have experiential knowledge and training. More specifically, CCAR describes a recovery coach as a motivator who exhibits bold faith in an/a individual/family's capacity for change, and who encourages and celebrates achievement. The recovery coach is an ally and confidant who genuinely cares, listens, and can be trusted with confidences, as well as a truth teller who provides a consistent source of honest feedback regarding self-destructive patterns of thinking, feeling, and acting. He or

she is also a role model and mentor who offers his/her life as living proof of the transformative power of recovery and provides stage-appropriate recovery education and advice. The recovery coach is trained to serve as a problem solver who identifies and helps remove personal and environmental obstacles to recovery. He or she serves as a resource broker, linking individuals/families to formal and indigenous resources such as sober housing, recovery-conducive employment, health and social services, and other recovery support. The recovery coach advocates by helping individuals and families navigate service systems for access, responsiveness, and protection of rights. The recovery coaches may also be community organizers to help develop and expand available recovery support resources, lifestyle consultants to assist individuals/families to develop sobriety-based rituals of daily living, and friends, providing companionship.[19] Coaches receive training at the CCAR Recovery Coach Academy, a 5-day intensive training program that focuses on providing individuals with the necessary skills to mentor, support, and guide any person who would like to enter or sustain long-term recovery from addiction. [20,21] At this training, prospective CCAR recovery coaches learn about the roles and functions of a recovery coach, core values and guiding principles of recovery, relationship enhancement and crafting skills, appropriate attitudes about self-disclosure, stages of recovery, addressing stigma, awareness of culture, power, and privilege, and addressing ethical and boundary issues. This Academy also teaches how to practice newly acquired skills.[20,21] CCAR recovery coaches' style of treatment is generally informal, and they assist the individual affected by OUD in focusing on what he or she can do at the present time to facilitate recovery in the future, in addition to helping these individuals connect with community resources. Reports suggest that fostering a supportive and positive treatment environment is critical.[22] Moreover, data suggest that trained peers with shared experiences have a higher success rate at engaging individuals needing help.[23,24]

Community paramedics and treatment of OUD.

Some small studies and anecdotal successes have been reported in a variety of settings when community paramedics were included in programs to assist patients with OUD. However, there have been no formal studies about the various possible roles of the paramedics or clinical outcomes. Most of the available reports are in EMS trade journals, organization newsletters, public news releases, and other "gray" literature. For example, a Fairfield County, Ohio initiative called Project Fairfield Overdose Response Team (FORT), dispatches a community paramedic and a law enforcement officer to meet with patients after opioid overdoses. This is a community outreach model program that contacts patients, within 1-3 days of overdose, and assists them with getting into treatment facilities, which are aimed primarily at abstinence. With no reports of formal outcomes, as of December, 2017, Project FORT had piloted 12 patients. Of these, 1 was known to be in an inpatient treatment program, and another had been admitted to the hospital for opioid withdrawal then discharged to inpatient treatment.[25] The Johns Hopkins Bloomberg School of Public Health is collaborating with Baltimore City Fire Department's paramedics and the Behavioral Health System of Baltimore in a program that trains the paramedics to perform a screening test for OUD, followed by a BNI after responding to opioid overdoses. At the time of their report, patients with OUD were being referred by the paramedics to a community-based research center within the Bloomberg School for counseling, motivation, and discussion of barriers to treatment. HIV (+) patients were preferentially referred to a medical facility for treatment with BUP along with management of their HIV disease. Their longer-term plan was to eventually transport clinically stable patients after overdose directly to a sobering center, similar to the protocol used in the City of San Francisco.[26] Although the patients referred by the paramedics to the community-based research center are randomized to one of 2 different treatment arms, there have been no reports of the effectiveness of the paramedics in this role. In a Palm Beach, FL community paramedicine program loosely based on previous work at Yale, consenting patients are started on BUP in the ED after an overdose. But community paramedics deliver the ensuing daily doses to the patients at home for the first week of therapy. These medics are accompanied by peer recovery specialists who work with the patient on support systems for longer term recovery. Although no outcomes data are available for this program, it involves a rapid taper off of BUP early in the treatment regimen. In most other studies, early discontinuation of BUP is associated with poorer short- and long-term outcomes, and increased risk of nonfatal and fatal overdoses.

The PRIDE program at Yale.

We previously demonstrated that 1/3 of all seniors who activated the local 9-1-1 system due to inability to get up after a fall at home would activate 9-1-1 again within the ensuing 30 days. Furthermore, 2/3 of all calls to EMS for a "lift assist" were repeat calls to the same address within the previous 30 days.[27] We therefore hypothesized that by addressing some of the factors contributing to the risk of falling, and by improving access to community medical resources based on individuals' needs, many unplanned health care encounters could be prevented, while keeping participants safely in their homes. Thus, a collaborative program between health educator (research) paramedics and home health care nurses was established at Yale by one of the co-PIs of the current proposal. The program was funded by a Health Care Innovations Award from the Centers for Medicare & Medicaid Services in 2014. The overarching goal of Paramedic Referrals for Increased Independence and Decreased Disability in the Elderly (PRIDE)[28] is to help older individuals to live independently, while decreasing requirements for unplanned utilization of EMS, EDs, and hospitalization. To be eligible to participate in PRIDE, seniors must have fallen in the past or feel they are at risk for falling, reside within a 15-town area in South-Central Connecticut, and reside at home or in an assisted-living facility. The program's intervention involves home visits by the PRIDE Team. Research paramedics record results of balance and other agility tests, participants' medications, vital signs, and perform safety assessments of the living space. The home health care nurses evaluate gait, posture, cardiovascular health and medications, requirements for durable medical equipment, and ongoing care needs, such as physical or occupational therapy. All participant data are entered into a HIPAA-compliant, encrypted database: Research Electronic Data Capture (REDCap®). Additionally, if needed, an appointment is made with the participant's primary care provider, and a ride in a medically appropriate vehicle to and from the appointment is included at no charge. Subsequent unplanned health care utilization is tracked using the electronic medical record system, EPIC, at YNHH. PRIDE has been operating for the last 4 years and has enrolled over 5,600 participants. Our interim data to date demonstrate that there are significantly fewer ED visits and less EMS utilization (Tables 1 & 2) among those who received PRIDE services, compared with participants who enrolled but declined visits by PRIDE staff. These data suggest that PRIDE's intervention is effective in decreasing unplanned health care utilization.

Follow up	No Intervention	PRIDE Intervention	p-value	% Change with Intervention
days since enrollment of intervention	$\frac{\textit{participants with} \geq 1 \textit{ unplanned health care encounter}}{\textit{total participants}}$		—	—
30 days	$\frac{429}{1759}$ (24%)	$\frac{373}{2841}$ (13%)	<0.001	-46
90 days	$\frac{520}{1327}$ (39%)	$\frac{613}{2352}$ (26%)	<0.001	-33

Table 1. Unplanned health care encounters with vs. without PRIDE intervention. For the "No Intervention group," "follow up" refers to the number of days following enrollment; for the "Intervention group," it refers to the 30-90 days following intervention.

Follow up	No Intervention	PRIDE Intervention	p-value	% Change with Intervention
days since enrollment of intervention	$\frac{\textit{participants with} \geq 1 \textit{ unplanned health care encounter}}{\textit{total participants}}$		—	—
30 days	$\frac{156}{980}$ (16%)	$\frac{100}{1285}$ (8%)	<0.001	-50
90 days	$\frac{174}{652}$ (27%)	$\frac{162}{980}$ (17%)	<0.001	-37

Table 2. EMS utilization among enrollees with vs. without PRIDE intervention. For the "No Intervention group," "follow up" refers to the number of days following enrollment; for the "Intervention group," it refers to the 30-90 days following intervention.

Proposed adaptation of PRIDE to serve persons with OUD.

We propose to adapt the PRIDE program infrastructure to provide a safety net for patients who 1) have been resuscitated from an opioid overdose with naloxone, 2) have screened positive for OUD using the MINI[29,30]

and 3) refused toinitiate treatment with BUP in the ED, if offered. We mayalso include and accept referrals from CCARproject alcohol & substance abuse services, education, and referral to treatment (ASSERT) (whose recruiters work in the YNHH ED), staff working in the Yale EDs and with American Medical Response (AMR) units, the Community Health Care Van (created by Dr. Frederick Altice), and from locations within the Elm City Communities (The Housing Authority of the City of New Haven).. For this program, the composition of the field teams will be changed, pairing recovery coaches from CCAR with experienced PRIDE research paramedics, to form RCP teams. For those affected by moderate-severe OUD, we expect that engaging with the RCP teams **will create a more robust linkage of care with community resources and treatment options.. Importantly, these teams will motivate interest in treatment, facilitate access to BUP or methadone, assist with other community-based recovery strategies, help address acute psychosocial issues, and provide ongoing education and counselling. The requirements for these capabilities were derived from our previous qualitative studies of persons with OUD who declined ED-initiated treatment.[11]**

How this project will improve scientific knowledge.

There has been extensive prior literature comparing treatment modalities for patients with OUD. In these studies, the arms are rigidly controlled to assess efficacy of the treatments. While BUP is currently considered the most effective treatment, many patients decline to start it after an overdose, and a substantial proportion of those who do start it do not achieve remission of their OUD. Less than half of patients who start it remain engaged in treatment at the time of follow up, though the proportion still engaged in treatment with BUP is roughly double that of the patients who are treated only with BNI or community referral. Investigators both here and in large, multicenter trials have found that outcomes of BUP therapy were not substantially improved by the addition of adjunctive counselling or cognitive behavioral therapy.[31-33] Adjunctive counselling was not shown to improve outcomes of patients on BUP in any of these studies. It should be noted, however, that the counselling was scripted and manual-driven to ensure consistency. Further, in one of the reports,[33] all patients were tapered off the BUP during the study with a predictable high relapse rate. Our study will demonstrate whether a more patient-centered approach, combining motivation to treatment while providing connections to continuous, community-based medical and psychosocial support, can improve outcomes compared with historical and concurrent controls. Positive findings in this study will further broaden the potential scope of mobile integrated health care, an emerging aspect of EMS. It may also reveal a synergistic effect of the traditionally community-oriented recovery model using peer coaches with the best medical management. If we find that our cohort of patients managed through this collaborative approach has improved outcomes, studies in the field will become even more complex, as it will be clear that interventions probably cannot be compared in isolation, but will be carried out with customized and adaptable supportive care.

Innovation.

This study employs recovery coaches, who have been trained by CCAR, and PRIDE health educator paramedics to form RCP teams. The goals of the recovery coaches are to promote recovery, remove barriers and obstacles to recovery, connect people with recovery support services, and help to build recovery capital while encouraging hope, optimism, and healthy living.[19] The specific mission of the research paramedics on the teams is to facilitate access to BUP, and help monitor patients' responses to the drug. They will assess for evidence of withdrawal, for resolution or persistence of craving, and for signs of opioid or other drug use, or intercurrent illness. From our previous experience with PRIDE, we believe that this team approach will have a synergistic effect on the missions of both members of the team, ultimately leading to improved outcomes for the patient. Fully integrated treatment with BUP along with individualized, sustained support by recovery coaches and community research paramedics has not been combined in formalized research protocols. Most research has focused on comparative effectiveness of individual treatment modalities. Importantly, in our study, the RCP teams will assist the patients with self-assessment and dynamic goal setting, so that MAT can be initiated whenever a patient is ready, and there is no set duration of BUP or any MAT. Premature tapering of MAT, regardless of other support services, is uniformly associated with high rates of relapse.

The RCP teams' support of persons with OUD will increase participant privacy and autonomy while working toward clinical remission and multi-dimensional recovery. Medical literature continues to support promoting these ideals across disciplines.[34-38] Moreover, privacy and stigma concerns frequently have been cited in the literature as significant barriers preventing some from receiving effective treatment.[39-42] In our program, BUP therapy will be prescribed and supervised in conjunction with a primary care medical clinic. The RCP team will meet by phone or video teleconference with participants who are in their homes or other locations outside of traditional medical institutions, and away from drug rehabilitation or methadone clinics to alleviate concerns about being seen at these places. Furthermore, participant autonomy will be promoted. Participants are not randomized blindly to a treatment arm, but instead select the treatment regimens that seem most consonant with their current needs. At any time, as circumstances evolve, the RCP teams will assist participants in changing into any other treatment option in the safety net cohort.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

To date, there is no standard of care for individuals with OUD who have overdosed on opioids, have been resuscitated by naloxone, and have refused BUP treatment. As noted in the previous section, YNHH typically will send home these individuals with OEN kits. However, follow-up care remains variable. Hence, we seek to determine whether individuals with OUD might benefit significantly from a novel, team-based intervention encouraging biopsychosocial and medical interventions. Our intervention will connect participants with important community resources that we expect will facilitate progress toward long-term recovery. Specifically, we will link individuals with moderate-severe OUD, who have experienced at least 1 opioid OD requiring naloxone resuscitation but who refused BUP treatment in the ED, if offered, with 1) treatment with BUP, 2) methadone maintenance, intensive outpatient, and/or residential treatment, or 3) education materials from CCAR. Enrolled participants may switch from 1)-3) throughout.

We wish to assess whether our intervention connecting participants to community resources affects 1) the frequency of secondary opioid OD events and 2) the proportion of individuals who remain engaged in treatment for OUD or are in remission at 30 days and at 180 days post consent. We define remission as engagement in daily medication-assisted MAT—typically BUP or methadone— and/or a recovery capital score of ≥ 27.5. Our hypothesis is that the intervention by the RCP team will decrease subsequent OD events and increase the likelihood of remission. We also seek to determine whether the intervention affects 1) the frequency of positive-urine tests for opioids and 2) the frequency and proportion of subjects self-reporting opioid use. Our hypothesis is that our intervention will decrease both.

We will conduct our study as follows (Figures 1 & 2 below):
To prepare for the intervention, health educator paramedics and key study staff are required to attend 12 hours of in-person training, which is to take place over at least 2 days, to learn about best practices assessing those with OUD. Dr. Michael Pantalon, co-PI of this study, along with CCAR staff, will teach. Sessions will include training to conduct a brief negotiation interview (BNI) and a brief assessment of recovery capital (BARC-10) interview. Training also will prepare all staff to respectfully ask questions about potential overdose events and the possibility of creating and/or implementing a wellness plan.

After resuscitation from opioid overdose by naloxone, affected individuals in the EDs at the York St. and Chapel St. campuses of YNHH will be screened for OUD using a MINI. As noted above, this is an evidence-supported, standard practice at our institution. Upon screening positive for OUD, individuals should be offered BUP treatment by staff. Those who screen positive for OUD, but who decline BUP, are offered overdose and naloxone kits. In addition, by using EPIC from the Department of Emergency Medicine / EMS

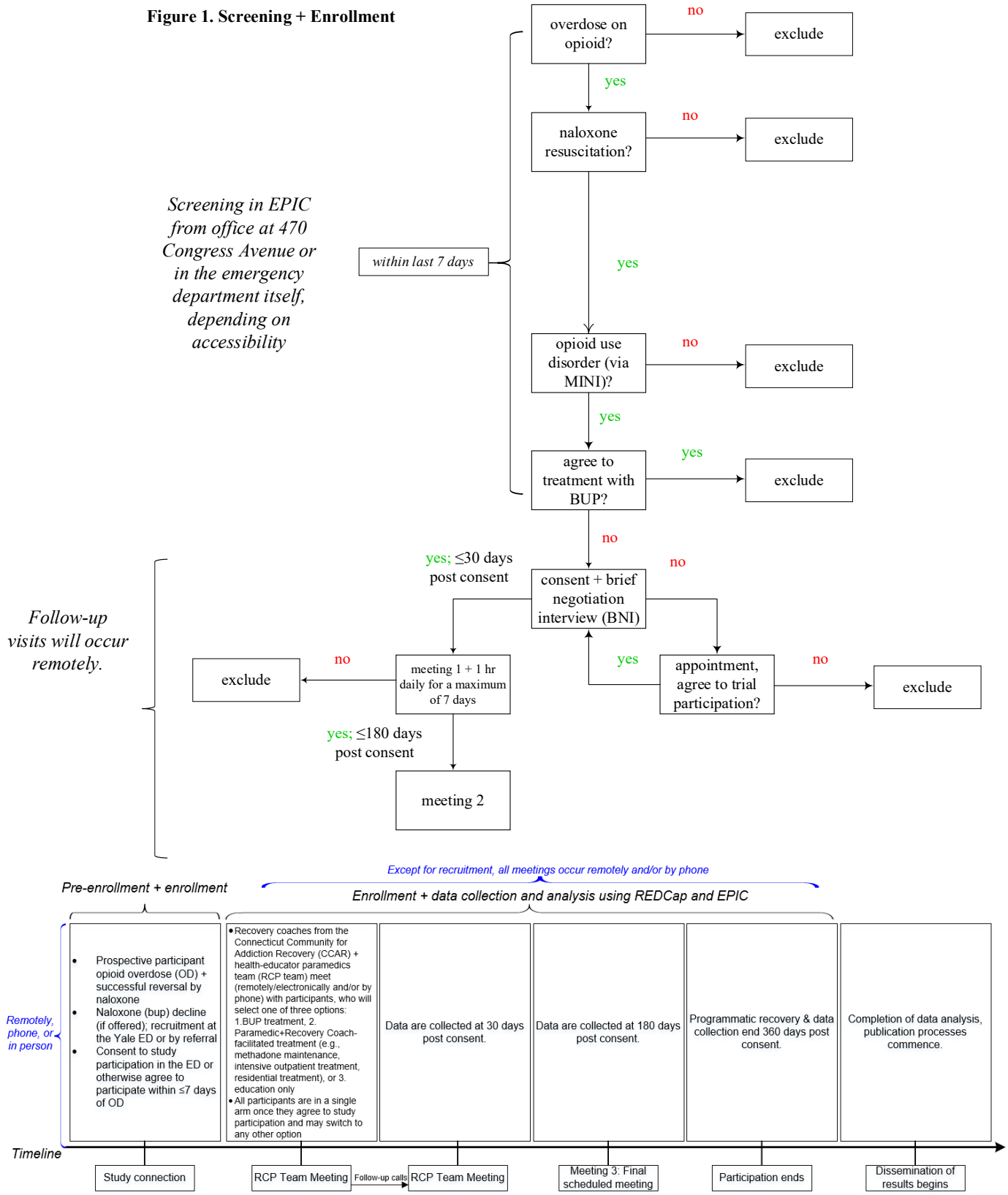
offices at 470 Congress Avenue in New Haven, CT, our study team will screen for resuscitated, OUD-positive individuals, who refused BUP, if offered, and may approach these individuals in the ED to ask whether they might be interested in research participation. To be clear, due to limitations imposed by the coronavirus pandemic of 2020, as of 06/02/2020 our team will screen for prospective participants from the office at 470 Congress Avenue and will only enter the ED to consent potentially eligible participants in person. If the prospective subject were to express interest in study participation, then the study team members would set up an appointment to meet remotely (by EPIC telehealth functions (if applicable), phone, Zoom 5.0, or other encrypted, HIPAA-compliant electronic modality) at a time of the prospective participant's choosing. Informed consent may be obtained by the RCP team in the ED or at the first electronic visit, although the latter is more likely given the constraints of ED accessibility at this time. In addition, ED providers and affiliates from AMR, staff from CCAR, Project ASSERT, Elm City Communications, and the Community Health Care Van may refer interested individuals to study participation, providing that at some time in the previous 7 days the prospective participant overdosed on opioids, were resuscitated by naloxone, and screened positive for OUD..

The RCP team will respect all safety precautions, especially those pertaining to the coronavirus pandemic, at all times. The team will respect social distancing and will don face coverings when using the office at 470 Congress. Personal protective equipment (PPE)— masks, gloves, gowns, and sanitizers as required by ED protocol—will be worn whenever appropriate.. All individuals who might work in the ED will undergo training in proper use, including donning and doffing the designated PPE.

Consent may be obtained at the ED, during community outreach events, electronically in a Yale School of Medicine version of REDCap®, or remotely (e.g., via email or picture), in accordance with University guidelines issued on 05/21/2020 from the Yale Center for Clinical Investigation. After consent and study initiation, either at the hospital or at some other time, the RCP team will perform a BNI— whose goal is to employ motivational techniques to help those with substance abuse consider their reasons for wanting to address dependency. Electronically, the RCP team will perform psychosocial and medical evaluations. (Please see the document, *Survey Tool and Handbook*, for details. It is included in our submission materials.) The RCP team will enter all data into a secured, encrypted database, REDCap®. To obtain consent or approximately 30 days after consent, the RCP team will schedule an electronic/remote (including by phone) Meeting 1 with participants. During this time, by remote interventions, the RCP team will collect and enter data into REDCap® based on discussions with and evaluations of participants. During an electronic/remote (including by phone) Meeting 2, which should occur no more than 180 days after consent, the RCP team will also collect and enter data into REDCap® based on discussions with and evaluations of participants. The study team will also enter data from participants' medical records at all time intervals. It is important to underscore that, due to the coronavirus pandemic, electronic and remote (including by phone) modalities will be utilized to the greatest extent possible.

Data from the entire cohort will be compared in aggregate with patients who were started on BUP in the ED over the same time period and with historic controls.[11]

Figure 1. Screening + Enrollment



Genetic Testing N/A ☒

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*

ii. the plan for the collection of material or the conditions under which material will be received *Write here*

iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*

iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*

C. Is widespread sharing of materials planned? *Write here*

D. When and under what conditions will materials be stripped of all identifiers? *Write here*

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*

F. Describe the provisions for protection of participant privacy *Write here*

G. Describe the methods for the security of storage and sharing of materials *Write here*

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Participants in this research will be those who are ≥18 years old and who have overdosed on opioids, have moderate-severe OUD disorder (determined by MINI), and have been resuscitated by naloxone..

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement. N/A

☐Children ☐ Healthy ☐Fetal material, placenta, or dead fetus

☐Non-English Speaking ☐ Prisoners (parolees + probationers incidentally enrolled only)

☐Economically disadvantaged persons

☐Decisionally Impaired ☐ Employees ☐Pregnant women and/or fetuses

☐Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

CRITERIA += *yes* -= *no* OUD= opioid use disorder	**POTENTIALLY ELIGIBLE?**	**EXCLUDE?**

1. Age ≥ 18	+	-
2. Screen positive for opioid use disorder (OUD)	+	-
3. Screen positive for OUD using mini international neuropsychiatric interview (MINI) (if applicable)	+	-
4. At least 1 opioid overdose requiring resuscitation by naloxone	+	-
5. Have a non-opioid overdose explanation for decreased level of conscientiousness, miosis, or decreased respiratory rate (if applicable)	-	+
6. Positive for OUD using a health questionnaire containing questions about prescription opioid and heroin use	+	-
7. Not in a critically ill state at the time of consent (e.g., not actively suicidal, psychotic, septic, and/or experiencing cardiac arrest)	+	-
8. 3.,4., & 6. (in this column) must have occurred within ≤7 days (inclusive) from date of consent if the prospective participant were immediately discharged from the emergency department (ED), floor, or other health care facility; consent may be obtained at any of these locations	+	-
9. Homicidal	-	+
10. Able to consent to program/study participation	+	-
11. Permanent residence is a long-term care/skilled nursing facility	-	+
12. Simultaneously enrolled in another study whose principal investigator (PI) or co-PI is a faculty member in the Department of Emergency Medicine	-	+
13. Prescribed opioids for acute pain, chronic pain, or palliative care without OUD	-	+
14. Stably enrolled in opioid agonist treatment or other medication-assisted therapy for OUD at the time of consent	-	+
15. In police custody or incarcerated (at the time of consent to participate or any known time after). (Parolees & those on probation may be eligible, but are NOT the target population and may be enrolled *only incidentally*.)	-	+
16. Refused buprenorphine/naloxone (BUP), if offered	+	-
17. Has a mailing address or P.O. box	+	-
18. Able to answer questions electronically/remotely (including by phone)	+	-

8. How will **eligibility** be determined, and by whom? Write here
   In general, eligibility will be determined by the RCP team. ED and study staff may assist occasionally.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
   Overall risks: Because the procedures involve accepted forms of treatment interventions, interviews, and self-report questionnaires, we foresee no special hazards. The principal risk to participants is that of ongoing illicit opioid use—including the potential for overdose. The instruments have been used in similar projects in the past with no ill effect. However, another important risk is the possibility that sensitive, confidential information obtained during the study will be disclosed. Given the social and legal sanctions associated with the use of opioids, it is critical to obtain a certificate of confidentiality, which the Centers for Disease Control and Prevention (CDC), our funding agency, has granted per section 2012 of the 21st Century Cures Act. We will clearly explain our mandated obligation to report incidents, as well as suspicion of child abuse or neglect, and risk of harm to self and others, and advise subjects that continued drug use alone does not require reporting to child protection services.

Nonspecific Risks: Risks from qualitative interviews, counseling, electronic medical record review, and rating scales are not beyond usual clinical procedures in drug treatment. Confidentiality of these results are specifically protected by federal law, and all records will be identified by code number only, with the master file kept under lock by the PI. The psychosocial interventions used in the study are based on principles of motivational interviewing and have been used in clinical programs without adverse effects. Any potential risks (e.g., discussion of upsetting events), however, will be minimized through the use of trained, experienced recovery coaches. Women of childbearing age will be included in the study. We have assessed the proposed study as one of minimal risk. Nevertheless, because of the study population, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur, since it is not possible to predict with certainty the absolute risk in the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study.

Also, as mentioned previously, the RCP team will respect all safety precautions, especially those pertaining to the coronavirus pandemic, at all times. The team will respect social distancing and will don face coverings when using the offices at 470 Congress. PPE— as required by ED protocol—will be worn throughout all study engagements. . All individuals who might work in the ED will undergo training in proper use, including donning and doffing of PPE, in addition to maintaining mandated hand hygiene and disinfection practices. There is limited possibility for in-person contact with study participants, so risks associated with the pandemic are minimized.

10. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized. (Please see above.)
11. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) Please see below for details.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for

This study is characterized as a clinical trial. Monitoring for data integrity and safety will be the responsibility of the investigators and the Yale Human Investigation Committee (HIC) (Yale's Institutional Review Board (IRB)). The principal investigators (PIs) will be responsible for monitoring data, assuring protocol compliance, conducting the safety reviews, and monitoring the specified frequency of the reviews at a minimum of every 2 months. During the review process, the PIs will evaluate whether the study should continue unchanged, require modification/amendment, continue, or close to enrollment. Either the PIs or the HIC has the authority to stop or suspend the study or require modifications. Adverse events will be monitored for each subject participating in the research and attributed to the study procedures/design by the principal investigators (Daniel Joseph, MD and Michael Pantalon, PhD) according to the following categories: 1. Definite: Adverse event is clearly related to study involvement. 2. Probable: Adverse event is likely related to study involvement. 3. Possible: Adverse event may be related to study involvement. 4. Unlikely: Adverse event is likely not to be related to study involvement. 5. Unrelated: Adverse event is clearly not related to study involvement.

Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study: 1. Mild adverse event 2. Moderate adverse event 3. Severe adverse event.

Plan for Determining Seriousness of Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes: 1. Death; 2. A life-threatening experience, in-patient hospitalization, or prolongation of existing hospitalization; 3. A persistent or significant disability or incapacity; 4. A congenital anomaly or birth defect; or 5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Plan for Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including Adverse Events) to the IRB:

The PI will report the following types of events to the IRB: Any incident, experience or outcome that meets ALL 3 of the following criteria: 1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; and 2. Is related or possibly related to participation in the research. (*Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and 3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized. These UPIRSOs/SAEs will be reported to the Yale IRB in accordance with IRB Policy 710, using the appropriate Yale forms. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 will be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is overseeing the study).

Plan for Reporting Adverse Events

For this study, the following individuals, funding, and/or regulatory agencies will be notified: all co-Investigators listed on the protocol, the Data Safety and Monitoring Board, the Yale HIC, and the Centers for Disease Control. The principal investigators (Daniel Joseph, MD, and Michael Pantalon, PhD) will conduct a review of all adverse events upon completion of every study subject. They will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required. The risks associated with participating in this study can be categorized as minimal. The Data and Safety Monitoring Plan (DSMP) template of the Yale University School of Medicine includes provisions for data review and performance of safety reviews, as described below. Data and safety monitoring procedures in this study include secure computerized data collection and monitoring systems and an organizational structure of clearly defined tasks assigned to all research and clinical personnel involved in the conduct of this study. The computerized study tracking system consists of a data base system that records research activities including enrollment and follow-up activities (assessments, urine collection, and treatment clinic attendance) and allows monitoring of drug use through inclusion of the results of urine toxicology testing. The PIs will use this database to monitor ongoing subject participation. The organizational structure used to ensure quality of data in this project include extensive training and close supervision of clinical staff and research paramedics in data collection, and preliminary review of collected data by study personnel for completeness and accuracy. Research paramedics will computerize collected study data using encrypted tablets with specialized software (Zoom 5.0. REDCap®, EPIC telehealth, SPSS Data Entry, etc.) facilitating efficient data entry and allowing elimination of out-of-range values and double entry of data for detection of key punch errors. All error corrections will be fully documented in the research records of the study. All research personnel are required to successfully complete the Yale Human Investigation Committee initial and ongoing training in protection of human subjects and the responsible conduct of scientific research. All clinical aspects of the study that take place in a YNHH ED, such as treatment delivery and monitoring of subjects' progress, are also fully documented and supervised by the PIs. Drs. Fiellin and D'Onofrio will meet monthly to review the overall progress of the patients receiving BUP treatment. All members of the research team are familiar with procedures for identifying and reporting possible adverse events.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? N/A

ii. What provisions are in place for management of interim results? N/A

iii. What will the multi-site process be for protocol modifications? N/A

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Study design

Primary outcomes

The primary outcomes will be 1) percentage of individuals with repeat opioid overdose events requiring naloxone resuscitation, identified using YNHH's electronic medical record system (EPIC), and 2) percentage of individuals engaged in any treatment for OUD or who are in remission. Data will be recorded at baseline and at 30 and 180 days after consent to participate in the research.

Secondary outcomes

The secondary outcomes will be 1) frequency and percentage of individuals with positive opioid tests (urine) recorded in their hospital charts or during medication program monitoring, and 2) frequency and percentage of subjects with self-reported opioid use. Data will be recorded at baseline and at 30 and 180 days after consent to participate in the research.

Statistical analyses

We will document demographics (sex, race/ethnicity, age, education, employment status, etc.) and clinical characteristics (e.g., heroin use, non-opioid use in the past 6 months, lifetime treatment for addiction etc.) among all cohorts. X^2 tests (2 df) will be employed to detect statistically significant differences.

Group	**X**	**No X**	**Total**
PRIDE + CCAR intervention			
BUP-initiated in ED after OD			
Historical control(s)			
Total			
For primary outcomes, "X" is % of repeated overdose events or % of treatment engagement. For secondary outcomes, "X" is frequency or % positive testing for opioid tests or % (self-reported) opioid abuse.			

Sample size determination

We estimate that data from approximately 100 individuals will be used. Recent data from American Medical Response (AMR) suggest that in 2017, 447 individuals have been transported to the YNHH ED for heroin overdose, and 136 others were documented as being treated in the ED. We expect that many of these individuals will elect to undergo BUP treatment in the ED, but that many others will enroll in our research. However, inevitably some will be lost to follow up. Power calculations are based on previously published data involving screening, brief intervention, and referral to treatment and the use of buprenorphine in primary care settings.[1,32,43] Findings suggest small-to-moderate (f=0.2-0.4) and moderate (f=0.5), respectively, effect sizes for these practices. Statistical power (1-β) will be 80%, and significance level (α) will be 5%.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.
Write here

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

B. DRUGS/BIOLOGICS ☒N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☐
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☐
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☐

4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☐
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
Write here

3. Source: Identify the source of the drug or biologic to be used. *Write here*

a) Is the drug provided free of charge to subjects? ☐YES ☐NO
If yes, by whom? *Write here*

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Write here

Check applicable Investigational Drug Service utilized:

☐ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation*.

5. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study.
Write here
c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
Write here
d) Describe the procedures that are in place to safeguard participants receiving placebo.
Write here

6. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☒ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. Though not a "study drug," an objective of this study is to maximize the use of BUP for OUD by connecting participants with community resources to obtain it. BUP is a commercially available drug that can continue to be prescribed by providers responsible for participants' ongoing medical care.

☐ NO If no, explain why this is acceptable. *Write here*

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☐No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms

requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
   Write here
3. **Source:**
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. Targeted for enrollment at Yale for this protocol: 100 participants total
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers (available in EDs for distribution)	☐ Internet/web postings	☐ Radio
☒ Posters (at CCAR and in EDs)	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review* for chief complaint while in ED	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Recruiters will review chief complaints in EPIC from an office at 470 Congress Avenue (an office that is close to the York Street ED). Our study team also will accept referrals from ED providers and affiliates such as the American Medical Response (AMR) transportation company, qualified mental health care professionals and trained recovery coaches at the CT Community for Addiction Recovery, and from individuals engaged with project ASSERT, who work regularly in Yale EDs. In addition, we will accept referrals from Elm City Communities (The Housing Authority of New Haven) and from Yale's Community Health Care Van.

b. Describe how potential subjects are contacted.

Prospective subjects will be contacted in person at the ED and/or electronically at a later time (depending on when someone might wish to consent to participation) of the prospective participant's choosing and by phone from a referral. Referrals from community outreach initiatives (see 3.a.) also will be accepted by the research team, who then will reach out, typically by remote/electronic modalities and/or by phone, to prospective participants.

c. Who is recruiting potential subjects?

The study team—health educator (research) paramedics, recovery coaches, a research associate, and trained mental health care professionals and counselors— will participate in recruitment. Staff from Chapel and York Street ED campuses, CCAR, Project ASSERT, Elm City Communities, and Yale's Community Health Care Van may refer eligible patients to the study team in real time when appropriate.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☒Yes, some of the subjects

☐No

If yes, describe the nature of this relationship. One of the co-investigators, Dr. Michael Pantalon, may refer patients from time to time. It is also possible that, if working in the ED, Dr. Daniel Joseph would refer a patient.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: Yale's EDs are fast-paced environments where new facts constantly emerge about any given case. The optimal and most practical way to identify prospective participants in this environment would be to scan for chief complaints on display boards and ED charts in EPIC. Obtaining prior authorization would not be practical. This is also true for all other referrals.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   Depending on preference informed consent may be obtained by the RCP team in the ED, in the community, or remotely at the first outpatient visit. All consent must be documented and given in writing. Consent may be documented electronically in a Yale School of Medicine version of REDCap®, or remotely (e.g., via email or picture), in accordance with University guidelines issued on 05/21/2020 from the Yale Center for Clinical Investigation.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   To assess capacity to consent, participants will be asked to answer several basic questions: e.g., the date, location, current President of the United States, etc. If consent cannot be obtained, then recruiters will ask permission to set up a meeting time when the research might be discussed further. During this meeting, the RCP team may consent the participant.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   Eventually, we expect to enroll individuals who speak Spanish only and thus will add a translated consent form.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. *Please review the guidance and presentation on use of the short form available on the HRPP website.*

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☒
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☒ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☒ Requesting a waiver of consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

- What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? Names, dates, telephone and/or FAX numbers, geographic data, email addresses, medical record numbers, and health plan numbers (if applicable). Collaborators

from Elm City Communities (the New Haven Housing Authority) may have access to de-identified data (including the number of residents from Housing Authority locations who either enroll in the study or are referred to other agencies (e.g., CCAR), and the number of program successes).

1.

2. How will the research data be collected, recorded and stored? Participants may sign hardcopy documents or consent via REDCap®. Study team members will enter participants' data into REDCap® (online database).

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? Consent documents will be kept in a locked, secured cabinet in the Department of Emergency Medicine at 470 Congress Avenue. All data will be entered into REDCap® (noted above) only. This is an acceptable platform for entering and storing sensitive information, including protected health information (PHI). Data will be entered into this site via iPads, laptops, and desktop computers.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.
Once the data are entered and all analyses are completed, eventually all data and consents will be destroyed after a maximum of 6 years from the study's completion (see HIC's investigator manual).

6. If appropriate, has a Certificate of Confidentiality been obtained?
Our research is funded by an R01 through the CDC, which no longer issues hardcopy Certificates of Confidentiality (CoCs). However, as noted above, per section 2012 of the 21st Century Cures Act, a CoC "automatically" has been issued by the agency. https://www.cdc.gov/od/science/integrity/confidentiality/applinst.htm

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
Participants are expected to directly benefit from the educational, counseling, and medical resources and contacts. We expect that this will provide better outcomes in the short- and possibly long-terms.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
Participants may decline study participation or participate in another study. BUP can be started in the ED for individuals willing to accept it at the time of an OD. Other resources for harm reduction and treatment are routinely provided at the time of an ED visit, but are seldom associated with positive short-term outcomes.

2. Payments for Participation (Economic Considerations): Describe any payments that will . made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
Participants will receive 3 payments of $25 (for a total of $75) after consent and after the first and second meetings. Each payment is given as a $25 gift card to Stop & Shop. Initial payments may be obtained upon consent in the ED; subsequent payments will be mailed or provided electronically, according to subjects' preferences.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
The research will not generate any costs to participants, as we expect that study personnel will meet with them at settings and times of participants' choosing and convenience. All medical and laboratory testing is part of participants' routine care and is not directly a feature of the research itself. Additionally, for those electing to receive BUP, grant funding will cover its cost.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

    a. Will medical treatment be available if research-related injury occurs? Yes.

    b. Where and from whom may treatment be obtained? Members of the RCP team (research paramedics and recovery coaches) are well trained in recognizing and handling a wide variety of medical concerns. Emergencies will be managed by activating the 9-1-1 system and having patients transported to the nearest ED.
    c. Are there any limits to the treatment being provided? No.
    d. Who will pay for this treatment? The participant's insurance provider or equivalent
    e. How will the medical treatment be accessed by subjects? As above.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☐ No ☐**

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐ No ☐**

c. Will a novel approach using existing equipment be applied? **Yes ☐ No ☐**

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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