Study Title: Chestnut Health Systems Justice Community Opioid Innovative Network Research Hub: Improving Retention Across the OUD Service Cascade Upon Re-entry From Jail Using Recovery Management Check-Ups (RMC-A) Experiment

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Clinical Trial Protocol and Statistical Analysis Plan

Version 1.0

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Section 1: Basic Information

1.1. Study Title: Improving Retention Across the OUD Service Cascade Upon Re-entry From Jail Using Recovery Management Check-Ups (RMC-A) Experiment

1.2. Study is exempt from Federal regulations: No

1.3. Exemption number: n/a

1.4. Clinical Trial Questionnaire:

1.4.a. Study involves human participants: Yes

1.4.b. Participants are prospectively assigned to an intervention: Yes

1.4.c. Study is designed to evaluate the effect of the intervention on the participants: Yes

1.4.d. The effect that will be evaluated a health-related biomedical or behavioral outcome: Yes

1.5. ClinicalTrials.gov Identifier: TBD

Section 2 - Study Population Characteristics

2.1. Conditions or Focus of Study: Opioid use disorders (OUD)

2.2. Eligibility Criteria

Inclusion criteria are:

(a) meets DSM-5 opioid use disorder criteria in the past year

(b) heroin or other opioid use in the 90 days prior to entering jail and

(c) is released from 1 of the participating jails.

Exclusion criteria include:

(d) is under age 18 or

(e) cognitive impairment that precludes ability to give informed consent, and

(f) resides outside the service area.

2.3. Age Limits

Min Age: 18 Years

Max Age: N/A (No limit)

2.4. **Inclusion of Women, Minorities, and Children**

Study participants will be recruited from individuals with opioid use disorders who are discharging from one of five jails within Illinois and are eligible for treatment with medications for OUD (MOUD). The numbers below are each based on information obtained from the participating OTPs about their admissions in the past year.

Women. We anticipate that overall 57% of study participants will be female. This distribution reflects the patient population in these participating OTPs as well as the broader population of patients seeking treatment within the targeted areas in Chicago. All efforts will be made to ensure that male and female participants are recruited into the study and Urn Randomization will be used to maximize the extent to which they are assigned to condition without bias or preference. This distribution is consistent with and justified by study scientific objectives and the proposed study design. Sex (female/male) will be included as a key moderator variable in the statistical analyses in order to estimate and compare intervention effects by sex, based on prior research findings that suggest sex differences in the outcomes of treatment in OTPs. Evaluation of study outcomes, as specified in the specific aims/hypotheses, and all statistical analyses will be conducted without bias regarding sex.

Minorities. We anticipate that the study sample will be 26% Hispanic; 49% African Americans, 25% whites, and 26% of mixed/other race. This distribution reflects the patient population in these participating OTPs as well as the broader population of patients seeking treatment within the targeted areas in Chicago. All efforts will be made to ensure that participants of all racial/ethnic groups are recruited into the study and randomly assigned to condition without bias

or preference. This distribution is consistent with and justified by study scientific objectives and proposed study design. The sample distribution includes at least 25% of each racial/ethnic subgroup, which will enable us to evaluate the extent to which the observed intervention effects are invariant (i.e., similar) by ethnicity and by race. Prior research suggests that there are differences in outcomes of treatment for OUD by race/ethnicity. Evaluation of study outcomes, as specified in the specific aims/hypotheses, and all statistical analyses will be conducted without bias regarding race/ethnicity.

Children Under Age 21. Participants will be adults, aged 18 and older, who are incarcerated in jail in Illinois. Of the six participating OTPs, none reported having any patients less than age 18, and only one reported having patients between ages 18–20 (2%). Although we will not exclude 18–20 year olds, adults are the focus of the treatment programs in this study, consistent with the study design and specific aims. It is unlikely that sufficient numbers of 18–20 year olds will be recruited to test for whether the effects are invariant between these young adults and older adults. Thus, the study sample reflects the population in the participating OTPs and is scientifically justified by the study's focus on incarcerated adults with OUD. Evaluation of study outcomes, as specified in the specific aims/hypotheses, and all statistical analyses will be conducted without bias regarding age group.

2.5 Recruitment and Retention Plan

Recruitment Plan

Phase I: In Jail Screen for Study Eligibility. The study team will use two methods that have been successfully used in prior studies to recruit eligible individuals from jail settings and to engage them in the study. In the first method, staff at the jail (these may be corrections staff, medical staff, or staff from contracted OTPs) will identify individuals who have already been assessed with OUD (as part of the jail's usual screening protocol), provide them with an overview of the study, and, for those interested in learning more about the study, will secure their permission for a study research assistant (RA) to contact the candidate, confirm their eligibility (based on age and residency), and discuss transportation to the research office upon their release. In the second method, the RA will meet with the candidate immediately following their release, briefly overview the study, and discuss transportation to the research office post-release. Both procedures will allow the study team to contact individuals who have initiated treatment with MOUD pre-release as well as those who are quickly released, and may not have initiated treatment with MOUD. The study procedures may vary across the different jail sites dependent upon the established procedures for screening individuals for OUD upon their admission and for engaging them into MOUD prior to their release.

Phase II: Re-entry Meeting, Baseline Data Collection and Randomization. To maximize timely participation in the initial re-entry meeting, participants will be transported to the research office and given a $45 gift card upon completion of the baseline interview. Using similar procedures in the RMC re-entry trial, from the date of release, 35% were enrolled within 2 days, 69% within 4 days, and 90% within 7 days (mean=4.2 days, S.D.=3.8 days). RAs will then provide a detailed description of the study, and for those who agree to participate, RAs will administer the informed consent, complete the baseline research interview, update the locator, notify the Research Manager to randomize participants, and schedule the next research interview. The Research Manager will use gRand Urn Randomization (Version 1.10[49]) to randomly assign participants to one of 3 conditions: control, RMC, RMC-A. Urn randomization adjusts the probability of assignment to each condition in ways that simultaneously minimizes differences in multiple stratification variables. The base rate will be set at 33% to each condition,

and software set to simultaneously balance assignment by the county, days of opioid use in the 90 days prior to incarceration, and probation status at the time of release. It will also take into account participant characteristics that have been previously associated with differences in retention and outcomes for treatment with MOUD, including sex,[45,51] age,[52-53] cocaine use,[54] and mental health problem severity.[55-57] Controlling for these factors further improves the study's statistical power. The Research Manager will enter the information into the program, generate the assignment, and inform the participant's RA of the assignment. Next, persons assigned to the RMC or RMC-A conditions will meet with a linkage manager.

Retention Plan

RAs will complete 90-minute enrollment and quarterly follow-up research interviews with participants in all conditions. Study participants will receive a $45 gift card - $35/interview and $10/urine test. To retain people in the study, the team will implement Dr. Scott's[58] structured follow-up model which has reliably produced over 90% follow-up rates across studies involving over 70,000 patients regardless of population, primary drug type including heroin, and over follow-up periods ranging from 3 months to 18 years. Steps include: (a) contacting participants within 24-48 hours of study enrollment to collect additional locator information and mailing a schedule card for the next interview, (b) tracking status of interviews and locator information in a secure data base, (c) assigning each case to a follow-up case tracker, (d) verifying locator data, (e) conducting outreach for unverified cases and discussing them at weekly meetings, (f) mailing thank-you cards to participants and collaterals, (g) scheduling follow-up appointments in advance, (h) mailing 3 and 6 week post-enrollment flyers, (i) implementing returned-mail procedures, (j) calling participants 6 weeks before appointment to confirm date and location (phone vs. research office), (k) conducting outreach for unconfirmed cases and reviewing them at weekly meetings, (l) completing follow-up interviews and scheduling next appointments, (m) implementing a no-show protocol, and (n) incentives for both completing the interview and urine drug test. Progress will be monitored with daily management reports.

2.6. Recruitment Status: Not yet recruiting

2.7 Study Timeline

Following this section are two exhibits that support the discussion of the study timeline:

- Exhibit 1. Project Timeline shows activities by project year and month, with associated number of subjects/activities per month where applicable.
- Exhibit 2. Data Collection Summary gives counts by year

Both exhibits show peaks in data collection and intervention work in years 2-4 that are common in experiments with multiple waves of intervention and data collection per person. Below is a section by section explanation of activities shown on the timeline in months from the award date (7/15/19).

Study Start-Up. During months 1 to 7.5, the team will convene the Chestnut Hub collaborative researchers and representatives from the participating jails and OTPs to review the proposal and finalize the design instrumentation, study methods, and schedule for reports. We will finalize the site-specific issues for recruiting study participants (i.e., referral to study team for eligibility assessment) and establish Business Agreements with the participating OTPs in order to collect data from treatment records. The study team will be trained on all instruments and study procedures, and study-specific software and databases will be developed. We will participate in required JCOIN workgroup activities and develop plans for common measures,

protocols or analytic approaches and methods for data transmission to meet JCOIN requirements.

Enrollment Interview and Randomization. The next row shows the expected rate (varying from 20-40 per month) of recruitment in months 8 to 33 to obtain the target sample size (N = 750). Note that the rate of recruitment is reduced beginning in month 15 to compensate for concurrent baseline and follow-up interviews that peak in interviews in years 3 to 4.

Follow-up Research Interviews. The next 8 rows show the quarterly follow-up assessments (3, 6, 9, 12, 15, 18, 21, and 24) – each starting and ending 3 months after the prior row. This is followed by the total number of interviews.

Check-ups. RMC and RMC-Adaptive will be provided in months 8 to 57 to 1/3RD of those randomized to each. For RMC the checkups will happen at months 1, 2, and the same time as each of the quarterly interviews (every 3rd month). For RMC-Adaptive, the schedule will be individualized but we anticipate an average of every other month.

Transportation; Round-trip transportation (typically via Lyft or Uber drivers) will be provided to all interviews and checkups between months 8 to 57. It is based on 90% of the number of interviews plus an additional 1/17th for RMC-Adaptive sessions occurring between quarterly interviews for the 1/3rd in this group.

Data Cleaning and Analysis. Data cleaning and analysis will be done continuously from months 8 to 60. This includes automated range checks and skip outs during on-line surveys, matching to field management records of what is expected to have been done, variable and preliminary/final analysis file creation for the DSMB reports and papers.

Data Safety Plan Reports and Review. A preliminary Data Safety Plan (DSP) will be submitted to the Data Safety Monitoring Board (DSMB) prior to field work in approximately month 6. Annual DSMB reports with preliminary data, psychometric, analyses of the direct effects, and any negative event forms will then be submitted to the DSMB for review approximately 2 months prior to the annual NIDA progress reports (months 23, 35, 47) and prior to publishing the main findings (month 57). Although not shown above, the DSMB, IRB and NIDA will also be informed about any unexpected serious adverse events within 48 hours.

Work on Preliminary Presentations and papers. Work on the study design presentation and paper will begin in month 10. Other papers based on baseline participant needs, psychometrics, and lessons learned about working better with patients still in need after 3 months will also be done through month 60.

Work on Main Findings. Work on the main findings will begin around month 53 when sufficient data have been accumulated from the follow-up assessments to begin preliminary analyses, with the goal of submitting it for publication between months 58 to 60.

Other JCOIN Cooperative Agreement Activities. Although not shown on the project timeline, the PI and Co-I's and other study partners will attend the planned 2 JCOIN steering committee meetings each year. We will work with the Coordinating Translation Center (CTC) on topics that might be appropriate for dissemination and the Methodological and Advance Analytic Resource Center (MAARC) to identify opportunities to collaborate on more detailed analyses than what we have proposed here.

Exhibit 1. Project Timeline

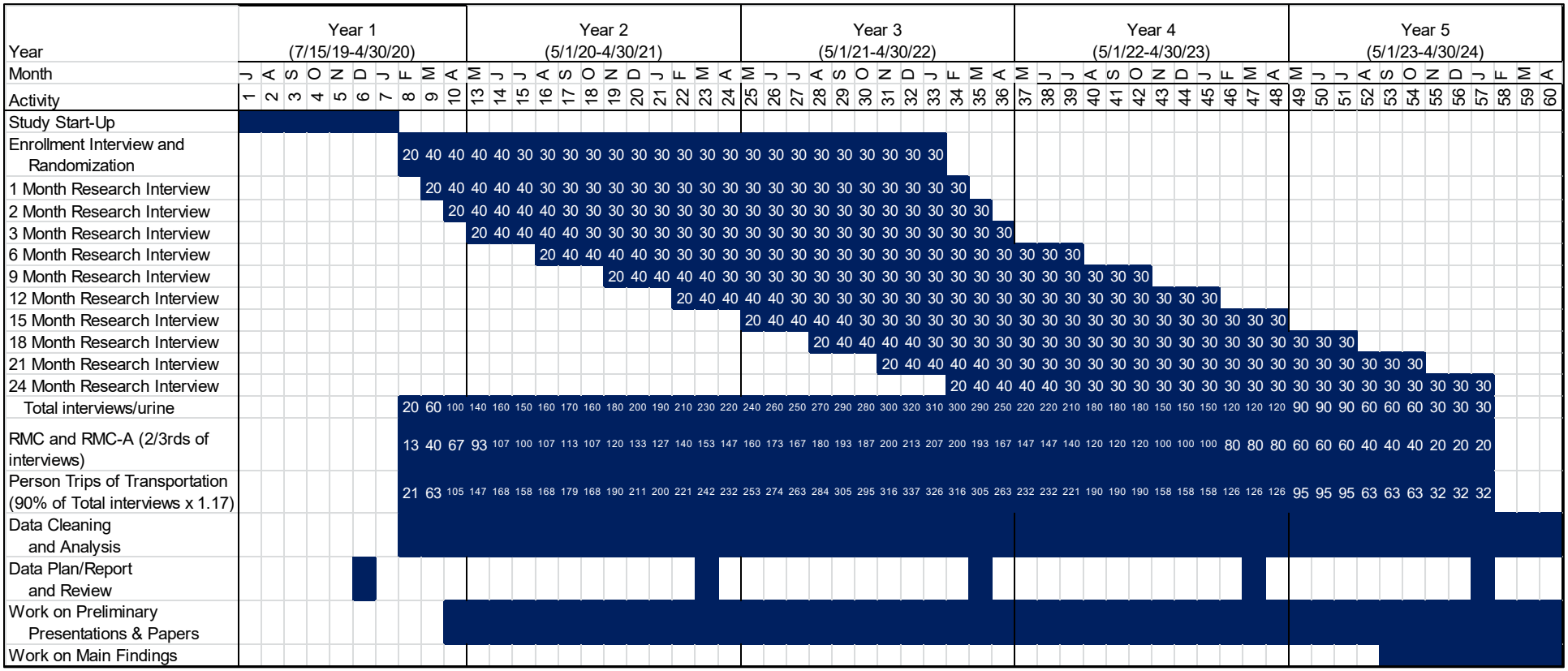

Exhibit 2. Data Collection and Intervention Summary

Field Staff Tasks	Hours	Year 1\c	Year 2	Year 3	Year 4	Year 5	Total
Enrollment Interview and Randomization		100	380	270	0	0	750
1 Month Research Interview		60	390	300	0	0	750
2 Month Research Interview		20	400	330	0	0	750
3 Month Research Interview		0	390	360	0	0	750
6 Month Research Interview		0	300	360	90	0	750
9 Month Research Interview		0	210	360	180	0	750
12 Month Research Interview		0	100	380	270	0	750
15 Month Research Interview		0	0	390	360	0	750
18 Month Research Interview		0	0	300	360	90	660
21 Month Research Interview		0	0	210	360	180	570
24 Month Research Interview		0	0	100	380	270	480
Total interviews/urine		180	2170	3360	2000	540	7710
Hours per interview/urine\a	7	1260	15190	23520	14000	3780	53970
Minimum FTE field work (Hour/2080)		0.61	7.30	11.31	6.73	1.82	25.95
RMC Q+ RMC Q (2/3rds of interviews)		120	1446.67	2240	1333.333	360	5140
Hours per RMC\b	3	360	4340	6720	4000	1080	15420
Minimum FTE for RMC(Hour/2080)		0.17	2.09	3.23	1.92	0.52	7.41
Person Trips of Transportation (90% of Tot		190	2285	3538	2106	569	8119
\a Average times to do recruitment, enrollment, collect & verifying locator data, randomization, tracking between interviews, actual interviews, saliva/ urine testing, field edits, data entry and provide transportation to research interviews.							
\b Average times per RMC to conduct BTNA, checkup, provide transportation/assistance to treatment, and follow-up to ensure treatment engagement/retention.							
\c 7.5 months (7/15/19 - 4/30/20)							

2.8. Enrollment of First Subject: March 15, 2020

Inclusion Enrollment Report: see following page

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ○ Yes ● No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Cook County, IL; DuPage County, IL; Grundy County, IL; McLean County, IL; Tazewell County, IL; Will County, IL

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	4	18	0	2	24
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	5	1	5	2	13
Black or African American	22	76	9	12	119
White	179	330	18	36	563
More than One Race	12	17	1	1	31
Total	222	442	33	53	750

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3: Protection and Monitoring Plans

3.1. Protection of Human Subjects

3.1.1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design.

Study Design. The goal of the proposed experiment is to compare linkage and retention rates as well as public health and public safety outcomes of 750 male and female detainees who will be randomly assigned to 1 of 3 groups upon their release from jail: a) re-entry as usual (control), b) the original Recovery Management Checkup (RMC) on a fixed schedule, and c) an RMC-Adaptive version in which the frequency and content of checkups will be based upon the participant's ongoing progress. The study will be conducted in collaboration with 6 county jails in Illinois (Cook, Dupage, Grundy, McLean, Tazewell, and Will) and the adjacent OTPs in each county. Pre-release participants will be screened for history of OUD. All participants will receive research follow-up assessments quarterly for 2 years which will also include urine testing and records checks (OUD treatment, mortality, recidivism). The specific aims are to evaluate:

Aim 1. The direct effects of RMC on the OUD service cascade of care (initiation, engagement, retention, and re-linkage, and months of MOUD treatment).

Aim 2. The indirect effects of RMC (via months of MOUD treatment) on public health outcomes (days of opioid use, OUD symptoms, quality of life and the cost-of-healthcare-utilization).

Aim 3. The indirect effects of RMC (via months of MOUD treatment and public health outcomes) on public safety outcomes (illegal activity, re-arrest, re-incarceration, and cost-of-crime)

Aim 4. The incremental costs and cost-effectiveness of the control vs. RMC vs. RMC-Adaptive in terms of both public health outcomes (days of opioid use, quality adjusted life years (QALYs), cost-of-health-care utilization) and public safety outcomes (re-incarceration and cost-of-crime).

Subject Populations

Inclusion criteria are: (a) meets criteria for DSM-5 opioid use disorder in the past year, (b) heroin or other opioid use in the 90 days prior to entering jail, and (c) is being released from 1 of the participating jails. Exclusion criteria include: (d) is under age 18 or (e) exhibits cognitive impairment that precludes ability to give informed consent, and (f) resides outside the service area.

To estimate the number of eligible individuals, we used a 2-step process. First, we obtained the number of people booked and charged in each participating county during 2016 (includes duplicated people) (109,422 bookings). Second, the 2017 National Survey on Drug Use and Health (NSDUH) data was subset to adults who had been charged and booked into a jail to estimate the rate of our target population that has a past-year OUD (11%). Based on this we expect 12,023 (11%) of the above bookings will involve people with OUD.

We further subset the NSDUH to those who had been charged and booked in jail AND had a past-year OUD as a proxy for eligibility for OUD treatment (to reflect the target population) and to estimate expected demographic characteristics. We anticipate that overall 34% will be female; 11% will be Hispanic; 75% white, 16% black; and 7% mixed/other race. We expect 5% to be ages 18-20, 26% ages 21-25, 48% ages 26-49, and 19% to be 50 to 64, and less than 1%

to be age 65 or older. OTPs estimate that about half of patients drop out of treatment within 3 to 12 months. About 10%-20% of the patients that drop-out are readmitted within one year.

Collaborating Sites

Research Sites

- The primary site for managing study recruitment, enrollment and delivery of interventions is Chestnut Health Systems, Lighthouse Institute, 221 W. Walton St., Chicago, IL 60610 under the supervision of Dr. Scott.
- The GAIN Q3 will be hosted at an internet co-location site at 303 E. Washington St., Bloomington, IL 61701 under the supervision of Dr. Dennis.
- All data will be downloaded, linked, cleaned, and de-identified at Chestnut Health Systems, 448 Wylie Dr., Normal, IL 61701 under the supervision of Dr. Dennis.
- Analyses using de-identified files will be conducted at the Chestnut offices by Drs. Scott and Dennis and their staff at the above addresses.
- A secondary site for managing the intervention is the sub awardee, American Institutes for Research (AIR), 10 S Riverside, Suite 600, Chicago, IL 60606, under the supervision of Dr. Salisbury-Afshar.
- Analyses of economic data will be done primarily at the University of Miami, Coral Gables, FL 33124, under the supervision of Dr. McCollister.

As part of the study design and specific aims, study participants will be recruited from six county jails in the Chicago Metropolitan Area / Cook County and central Illinois:

- Cook County Department of Corrections, 2700 S. California Ave., Chicago, IL 60608
- DuPage County Jail, 501 N. County Farm Rd., Wheaton, IL 60187
- Grundy County Jail, 111 E. Illinois Ave., Morris, IL 60450
- McLean County Detention Facility, 104 W. Front St., Bloomington, IL 61701
- Tazewell County Jail, 101 S. Capitol St., Pekin, IL 61554
- Will County Adult Detention Facility, 95 S. Chicago St., Joliet, IL 60436

The experiment will attempt to improve the rates of linkage to and retention of individuals who are released from each of these jails and are referred to their affiliated OTPs:

- Cook County Health and Hospital Systems (CCHHS), 2800 S. California Ave., Chicago, IL 60608
- Amita Health, 740 Pasquinelli Dr.,Westmont, IL 60559
- Family Guidance Centers, 2400 Glenwood Ave., Joliet, IL 60435
- Chestnut Health Systems, 702 W. Chestnut St., Bloomington, IL 61701
- Gateway Foundation, 11 S. Capitol St., Pekin, IL 61554
- Family Guidance Centers, 2400 Glenwood Ave., Joliet, IL 60435 (serves both Grundy and Will County from the same facility)

All OTPs are licensed by the State of Illinois Department of Health Services, Substance Use Prevention and Recovery Division (IHS/SUPR) to provide medication-assisted treatment for individuals with opioid use disorders in accordance with state and federal guidelines. These programs will: a) coordinate with the research team regarding information on case flow and treatment admissions and alert the study team regarding potential study participants who consent to meeting with project staff; b) utilize appropriate releases obtained via (1) Business Agreements between our agencies and (2) during a research consent process with participants; c) share the following information from study participants' treatment files with the study team: dates of admission, dosing days and amount, missed doses, date of discharge (if relevant) and

reason for discharge; and d) maintain regular communication with the Linkage Managers about appointments, no shows, and utilization.

b. Study Procedures, Materials, and Potential Risks

Materials. The primary sources of material include:

All participants:

- Interview Data. Face-to-face Interviews conducted at study enrollment at release to the community and quarterly follow-ups for 2 years post study enrollment. These interviews will consist of the *Global Appraisal of Individual Needs* (GAIN), quality of life measures from the *Patient Reported Outcomes Measurement Information System* (PROMIS)-R, and several study specific questions.
- Urine Tests. To increase the validity of self-reported opioid and other substance use, at the time of each in-person research assessment, on-site urine screens will be conducted with DrugCheck cups and fentanyl test strip using an immunoassay for rapid (2–5 minutes) qualitative results based on SAMHSA-standard cutoffs for any kind of heroin/morphine/ opioids in general (at 2000 ng/ml), 5 other specific opioids (Buprenorphine, Fentanyl, Heroin/Opioid 2000, Methadone, Oxycodone, Tramadol) and 10 other drugs (Alcohol, Amphetamine, Barbiturates, Benzodiazepines, Cocaine, Ecstasy, Marijuana, Methamphetamine, Phencyclidine, Synthetic Marijuana). Each of these tests has 98%+ accuracy, as well as temperature and validity strips to check for 6 types of adulterants (oxidants, specific gravity, acidity, nitrite, glutaraldehyde, creatinine). On-site urine test results will be shared with participants before asking questions about their recent substance use.
- Treatment Records Data. Each collaborating OTP will be asked to sign a Business Associate Agreement to collaborate with researchers on the extraction of information from patient records on their admission dates, treatment received, discharge dates, and discharge status. Each participant will also be asked to sign a release for parallel treatment data from any other OTPs or other MOUD treatment providers, including physician office-based practice with buprenorphine or naltrexone, or other outpatient or residential SUD treatment programs from which they receive treatment. Consistent with prior trials and current studies, OTPs will provide weekly treatment updates.
- Death Records Data. With the help of the State of Illinois and respective County Departments of Public Health, the research team will obtain information from the County Medical Examiner's office when applicable on participants who are suspected to be deceased and/or who could not be located for the final follow-up.
- Justice Records Data. With the State of Illinois' Law Enforcement Agencies Data System and help of each participating jail, we will abstract information on the charges, admission and release dates from jail at the time of recruitment through 24 months post-release. Across state and local official records and self-reports, in our prior studies these measures were largely consistent (kappa = .64), with each source identifying some unique cases of re-arrest or incarceration.

Participants in the RMC and RMC-Adaptive Conditions:

- Brief Treatment Needs Assessment (BTNA). At the beginning of each check up in the two RMC conditions, participants will be asked to complete a Brief Treatment Needs Assessment (BTNA) to facilitate the intervention. The BTNA includes sections on a) need for treatment (i.e., weekly or more frequent substance use since the last assessment, any past month SUD symptoms, or a current self-perceived need for treatment; alpha=.85; Test-retest Kappa=.78), b) potential barriers to treatment access, c) motivational readiness for

treatment, d) non project related re-entry services, and e) current treatment and incarceration status

- Digital recordings of all RMC and RMC-A linkage meetings and RMC-Adaptive case conferences will be made and 10% will be reviewed and rated for fidelity to their respective strategies. The number of linkage meetings and case conferences, and the participants at each, will be documented.

Potential Risks. The main risks associated with this study include: a) the possibility of unauthorized disclosure of sensitive information collected by research staff during interviews conducted at study enrollment and follow-ups; b) the possibility that interview questions may raise some psychological discomfort for the individual regarding their past or current substance use; and c) the potential discomfort about being asked about their past criminal behavior involvement.

During the research protocol and interviewer trainings, the PI will be very clear that if participants are uncomfortable with any question then the participant does not need to respond. The interviewing protocol also requires interviewers to contact their supervisor or PI immediately if such instances arise, so they can check in with the participant to determine whether the participant needs assistance. Participating OTPs also provide clinical backup when needed. In addition, participants are informed that if they report a recent situation involving child or elder abuse or neglect, these will be reported to the appropriate authorities. The appropriate authorities are also contacted in situations involving threat of harm to self or others.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent. Extensive training will be provided by the study team to ensure that the study protocols are implemented in a uniform manner and that all human subject requirements are observed. As part of the informed consent process, research staff will provide participants a copy of the informed consent document, read through it, provide them time to ask any questions, address the questions, and solicit their voluntary consent. The consent process includes specific releases regarding: (1) audio-recording of RMC sessions if they are randomized to the RMC or RMC-Adaptive conditions, (2) the strategies that will be used to locate them for follow-up interviews, and (3) permission to obtain information from the jail about subsequent recidivism and their OTP or other SUD treatment provider about admission, discharge and services received (if applicable). Participants will also be informed that the data collected as part of this study will be shared, without any identifying information, with NIH and the JCOIN project for analyses. If they agree, they will be asked to provide oral and written consent while being digitally recorded. Participants will also be asked for their consent to contact them for the follow-up interviews and urine tests scheduled for 3, 6, 9, 12, 15, 18, 21 and 24 months post-study enrollment. Whenever possible, follow-up interviews will be conducted at the Lighthouse Institute or OTP offices. If participants no longer reside in the county in which they were incarcerated and/or receive treatment, or have become re-incarcerated, follow-up interviews will be conducted by telephone. A detailed locator form will be completed at the time of study intake and it will be updated at each contact. There will be no penalties for anyone choosing not to participate. Participants will be compensated $45 for assessment ($35 for each 45–60 minute interview and $10 for each urine screen), for a potential total of $495 for completion of all 11 interviews.

b. Protections Against Risk. The investigators and senior staff have all completed the required Human Subjects and HIPAA training in protecting people and their privacy during a research study and are under the supervision of Chestnut's IRB. The project will also have an independent Data Safety Monitoring Plan. Because there is the risk that some participants might

be in jail or prison at some time during the follow-up period, the IRB has a prisoner representative, and we will secure approval from the NIH Office for Human Research Protections (OHRP) as well as secure a certificate of confidentiality from NIDA. All key research staff at CHS are or will be trained on the principals and process of informed consent through NIH's OHRP online training program (https://phrp.nihtraining.com/users/login.php) and then tested by their supervisors. They will also be required to complete NIDA's training on good clinical practice (GCP) for clinical trials (https://gcp.nidatraining.org/). All informed consents will be audiotaped for random review. If problems arise from the review, the PI and supervisors will meet with staff to correct the problem and meet with the participant when needed to clarify any potential confusion.

All staff involved in data collection will be trained on human subject protections and procedures and will provide written agreement to maintain the confidentiality and privacy of the information. Data will be managed by research staff via a secured web application that uploads each webpage view from the PCs (interviews and urine results). This application was developed by and is managed by Chestnut's GAIN Coordinating Center using a co-location site (i.e., an actual node on the internet vs. a connection to the internet). The software can be used for online interview while on the phone, when conducted in person, and/or for data entry. It uses secured sockets (like a bank), individual password and role authorization, auditing of all access/changes, and requires a two-way secure exchange to download data. The current generation of web-based software was implemented in 2008 and is updated quarterly; as of 12/30/18, it had been used to collect 893,846 GAIN interviews by 16,590 staff from 1,349 agencies.

When starting an interview, research interviewers can see a list of who is participating (in order to link records) but not their responses to earlier interviews. Once an interview is completed, only the Project Coordinator, Supervisors, Data Managers and IT support staff can see the responses to earlier interviews. All access to the system and to individual data is automatically logged and the audit trail is reviewed regularly for any inappropriate access. Confidential fields (e.g., names and other personal identifiers) are marked and not downloadable or visible to data managers. Data managers download, clean, and merge data using research ID and dates. They then replace the research ID with a second (randomly assigned) linkage ID, convert all dates into "days from randomization," and check all verbatim fields and remove any unexpected names or identifiers. These de-identified files are then used by scientists for analysis.

With regards to the participating OTPs, each will obtain permission to release information from patient records to Chestnut Health Systems, in accordance with the Health Insurance Portability and Accountability Act of 1996, Public Law 104-191, as amended, and the Privacy, Security, Breach Notification, and Enforcement Rules promulgated thereunder at 45 C.F.R. Parts 160 and 164 (collectively, "HIPAA"). Under HIPAA, "covered entities", generally defined as providers of health care services, may share personal health information of individuals they serve with other entities for certain purposes. This permissible arrangement under HIPAA will be documented by a "Business Associate Agreement". The Business Associate Agreement will set forth the purposes for which each Department may share individuals' personal health information with Chestnut Health Systems/Lighthouse Institute, specify HIPAA-compliant safeguards that Chestnut Health Systems/Lighthouse Institute will take to ensure the privacy of personal health information, and prohibit further disclosure of such personal health information. Further, each Business Associate Agreement will contain "qualified service organization" language, consistent with the Federal Regulations on the Confidentiality of Substance Abuse Patient Records found at 42 C.F.R. Part 2. This language is similar in nature to the business associate language discussed above but focused on the unique privacy safeguards for substance abuse patient records.

All PCs and web/server applications include password protection. Both use technical safeguards mandated by Health Information Technology for Economic and Clinical Health Act (HITECH) of 2009 for the transmission and maintenance of protected health information (PHI) and personal health records (PHR). As noted above, this includes using two-way encryption, check sum, double-keying, message authentication, digital signature, Secure Sockets Layer (SSL), and password-protected accounts that define levels of access. The possibility of risk regarding confidentiality will be minimized by stripping all participant identifying information such as name, driver's license number, and social security number from all interview notes and electronic data files. Electronic study information will be kept on a file server that is secure, encrypted, and protected by password. Only authorized staff will be allowed to see this information. Any study information that is kept on paper will be kept in a locked cabinet in a secure place. At the end of all study activities, the Chestnut Health Systems' research team will destroy all information that can identify participants.

The data security officers have also been identified for both CHS's GAIN ABS interview applications (Barbara Estrada) and all of Chestnut's corporate systems (Jeff Koski). Responsibilities of the security officers include developing information technology (IT) security policies, increasing security awareness for all project staff, providing virus protection for IT resources, maintaining security patches on computing equipment, developing and implementing back up procedures, performing periodic vulnerability scanning on IT equipment, reviewing and updating firewall strategies and policies, and enhancing the physical security of IT resources.

c. Vulnerable Subjects. Individuals who have a history of OUD, as well as involvement with the criminal justice system are considered to be vulnerable subjects. Thus we have explicitly proposed including an additional data safety plan. Chestnut's IRB also includes substance use treatment clinicians and prisoner representatives to provide additional perspectives related to how we explain the study activities, eligibility for study participation, the participant's rights, the consent process, protections taken to protect participants from any identified risks, and the balance of risks and benefits.

All three groups (including control) will have access to treatment for OUD as usual by the jail's primary provider or other providers. RMC has previously been shown to be effective with people who have SUD and for SUD treatment in general; however, the RMC model has not specifically been tested with a focus on individuals who have OUD and are involved with the criminal justice system with regard to its effectiveness in treatment linkage and engagement and on the specific study outcomes. Thus we have included a replication of RMC with this population as the middle condition. While we have presented preliminary evidence suggesting that there is considerable heterogeneity in how fast people respond to RMC, and have proposed to test a varying schedule of RMC check-ups in the RMC-A condition, we have included several safeguards against reducing the treatment dose to a level that has unintended consequences for the participant's sustained recovery. Specifically we will only increase the interval between RMC-A checkups at one-month increments and up to a maximum interval of 5 months. The latter would only occur after 5 checkups in a row without assessed need at the prior check-up. According to the proposed schedule of RMC-A check-ups, if an individual is not assessed as having a need for treatment at any of the scheduled check-ups, he/she will still receive a minimum of 5 checkups over 2 years.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

Participants may benefit directly by receiving an intervention (RMC or RMC-Adaptive) that helps them to initiate and stay in treatment, to reduce their risk of relapse to opioid use and overdose, to reduce their use of other substances, and to sustain recovery. At each study

assessment participants will be compensated at a rate of $45 per assessment ($35 for completing the interview and $10 for proving a urine sample) for a possible total of $495 for a total of 11 interviews over 2 years.

Participation may also benefit other people in the future by helping the field learn more about factors that reduce their risk of relapse to opioids and overdose, and/or other substance use, and drop-out of treatment and that promote their sustained treatment retention and improvements in quality of life and overall psychosocial functioning, ultimately leading to reductions in opioid-related morbidity and mortality and improvements in physical and mental health status. For this sample these may also combine to reduce recidivism and improve other public safety outcomes.

4. Importance of the Knowledge to Be Gained

Opioid use disorders are chronic conditions that have high risk of relapse and are associated with poor clinical outcomes, including relapse to opioid use and opioid-related overdose, use of other substances, treatment drop-out, and associated high rates of illegal activity and recidivism. Successful engagement and retention in treatment with MOUD are essential for improving patients' public health and public safety outcomes. If the experimental trial demonstrates the effectiveness and/or cost-effectiveness of RMC or RMC-Adaptive relative to re-entry as usual or relative to each other, this information will have important implications for reducing risk of relapse to opioid use following re-entry from jail, reducing the risk of opioid-related overdose, and improving jail and MOUD treatment outcomes, which can be widely generalized beyond the immediate study community to other jails/OTPs and potentially broadened to address other patient populations with OUD.

3.2. Multi-site study that will use the same protocols to conduct non-exempt human subjects research at more than one domestic site: Yes

3.3 Data and Safety Monitoring Plan

The process for determining whether an adverse event occurs, and for classifying it as unexpected, and/or possibly related to participation in the research study, and/or as series, will entail continuous review of information collected from study assessments, the participating OTPs, and administrative records that are relevant to the status of study participants.

Definitions of critical events to be monitored are:

• The expected Adverse Events (AE) measured directly as part of quarterly observations are the days of problems from SUD use, health problems interfering with responsibilities, mental health problems interfering with responsibilities, being disturbed by memories, behavioral problems, being homeless, family problems, illegal activity, arrests, in trouble with parole/probation.

• The expected Serious Adverse Events (SAE) measured directly as part of the quarterly observation are any medical ER/hospitalization, any mental health ER/hospitalization, and any re-incarceration. Deaths are documented both in follow-up logs and (if we have firsthand or reliable information) in the negative event report discussed below.

• Unexpected AE/SAE (including deaths where we have details) will be documented the same day we are informed with the negative event report. This includes documentation to code who was there, when/how it happened, where it happened, what actions were taken (e.g., referral to clinical supervisor, police report, hotline call).

In terms of timing, the DSM Plan will be reviewed by the IRB and funder prior to starting fieldwork. Annual reports of data collected to date (including case flow, checks on randomization, implementation, method checks on measures, preliminary outcome analyses, expected and unexpected AE/SAE, and all negative event forms) will be reviewed by the PI and used to generate our annual progress report to DSMB, IRB and NIDA. If any review reveals a significant difference in AE, SAE, or dependent variables that go AGAINST the experimental condition or appears to be related to a study specific procedure, we will consult with the IRB regarding the need to modify the protocol, study procedure, or stop the study. The stopping rule would be based on a statistically significant ($p<.05$) and clinically significant ($d<-0.2$) in the wrong direction.

Note that all unexpected AE/SAE and actions taken will be documented on the negative event form and reviewed within 48 hours by the PI (who will classify the incident as a SAE, AE, or other), the degree to which it is related to intervention or research procedures, and document any actions taken (with client, reporting to IRB). Any SAE or other events that are attributed to the intervention or research procedure and any sentinel event will be reported with 48 hours to the IRB and NIDA project officer for further review. For sentinel events, we follow the Joint Commission definition of a sentinel event as "any unanticipated event in a healthcare setting resulting in death or serious physical or psychological injury to a patient or patients, not related to the natural course of the patient's illness." (See https://www.jointcommission.org/assets/1/18/Sentinel%20Event%20Policy.pdf)

3.4 Data and Safety Monitoring Board

We will use the JCOIN DSMB convened by NIDA.

Section 4: Protocol Synopsis

4.1 Brief Summary

This project aims to complement HEAL's Justice Community Opioid Innovation Network (JCOIN) initiative by focusing on post-release recovery in 6 Illinois county jails with the goal of increasing linkage to and retention in community based Medication Assisted Treatment (MAT), and reducing both opioid use disorder (OUD) relapse and criminal recidivism over 2 years. We will conduct a randomly controlled trial comparing: a) re-entry as usual, b) Recovery Management Checkups (RMC), and c) an adapted version of RMC, RMC-A, that varies the intensity of recovery monitoring based on the person's need for treatment.

The Nation's Justice System provides a unique opportunity to help address this crisis as the justice population has a significantly higher rate of OUD than the household population, with roughly 1 in 4 people with OUD passing through the justice system each year. Re-entry into the community is a critical intercept point for linkage to opioid treatment programs (OTP), as there is ample evidence that the risk of relapse peaks in the initial period following release. Yet research has shown that only 25 to 50% of those receiving justice referrals to community-based OTPs or other providers of MOUD initiate treatment within 90 days. Justice referrals are also significantly less likely than non-justice referrals to remain in treatment for OUD for 90 days or longer. The combination of high rates of OUD and low treatment linkage and retention rates following release underscore the importance of improving the transition between incarceration and community-based treatment.

To date, 3 randomized controlled trials have demonstrated RMC's effectiveness by increasing treatment engagement and retention in substance use treatment (not focused on treatment with MOUD), re-linking recovering participants to treatment when indicated, and improving their treatment outcomes. Relative to controls, participants in the RMC condition reported more

treatment initiation, more days of treatment, fewer days of substance use, and fewer health symptoms overall. Within the RMC condition of the 3rd trial, there was considerable variation in how quickly people responded to checkups, as well as their pattern of treatment need over time. This trial provided a large enough subset of detainees (n=101) with OUD re-entering the community from jail and enrolled in RMC to examine multiple predictors of treatment need during two time periods, monthly and quarterly. In both cases, the best predictor of future need for treatment was the participant's need for treatment at the prior two checkups. Relative to RMC participants not in need of treatment, RMC participants who needed treatment in the prior 2 monthly checkups were almost 5 times more likely to "need treatment at 6 months post-release". Likewise, between 12 to 24 months, RMC participants who needed treatment at either of their two prior quarterly checkups were almost 18 times more likely to need treatment at the next checkup. These findings suggest that tailoring the checkup frequency to the individual's need for treatment may help target resources to those in need and reduce the burden on those with lower need, thus resulting in an improved overall effectiveness and cost-effectiveness of RMC checkups.

The goal of the proposed experiment is to compare linkage and retention rates, as well as public health and public safety outcomes of 750 male and female detainees who will be randomly assigned to 1 of 3 groups upon their release from jail: a) re-entry as usual (control), b) the original RMC on a fixed schedule, and c) an RMC-Adaptive version in which the frequency and content of checkups will be based upon the participant's ongoing progress. The study will be conducted in collaboration with 6 county jails in Illinois and the organizations approved to provide pre- and post-release MAT. Pre-release participants will be screened for history of OUD. All participants will participate in baseline and quarterly research interviews for 2 years, which will also include urine testing and records checks (OUD treatment, mortality, recidivism). The specific aims are to evaluate: 1) The direct effects of RMC on the OUD service cascade of care (initiation, engagement, retention, and re-linkage, and months of MOUD treatment); 2) The indirect effects of RMC (via months of MOUD treatment) on public health outcomes (days of opioid use, OUD symptoms, quality of life and the cost-of-healthcare-utilization); 3) The indirect effects of RMC (via months of MOUD treatment and public health outcomes) on public safety outcomes (illegal activity, re-arrest, re-incarceration, and cost-of-crime); and 4) The incremental costs and cost-effectiveness of the control vs. RMC vs. RMC-Adaptive in terms of both public health outcomes (days of opioid use, quality adjusted life years (QALYs), cost-of-health-care utilization) and public safety outcomes (re-incarceration and cost-of-crime).

4.2 Study Design

The RMC experiment will be conducted in collaboration with 6 jails representing discrete geographic counties in Illinois and the OTPs that serve them. It will compare a re-entry as usual control group with two experimental groups in terms of their impact on the OUD service cascade, as well as public health and public safety outcomes. Five participating jails provide MOUD for inmates with OUD prior to their release and the sixth will begin offering it later this summer. At the time of their release to the community, 750 men and women will be randomly assigned to 1 of 3 groups: a) a re-entry as usual control, b) RMC with monthly checkups for 3 months post-release followed by quarterly checkups up to 2 years, or c) an adaptive version of RMC (RMC-A) that includes a modified checkup schedule based on each individual's pattern of treatment need. All participants will complete research interviews at release and quarterly thereafter up to 2 years post-enrollment.

Study Aims and Hypotheses

Aim 1. The direct effects of RMC on the OUD service cascade (initiation, engagement, retention, and re-linkage, and months of MOUD treatment).

H1a. Relative to the control group over 24 months, the participants in the two RMC groups will be more likely to initiate MOUD and participate in MOUD treatment more months.

H1b. Relative to the RMC group over 24 months, the participants in the RMC-Adaptive group will be more likely to initiate MOUD and to participate in MOUD treatment more months.

Aim 2. The indirect effects of RMC (via months of MOUD treatment) on public health outcomes (days of opioid use, OUD symptoms, quality of life and the cost-of-health-care utilization).

H2a. Relative to the control group, the participants in the two RMC groups will have better public health outcomes (fewer days of opioid use, fewer OUD symptoms, better quality of life, and lower cost-of-health-care-utilization) in the next quarter.

H2b. Relative to the RMC group, the participants in the RMC-Adaptive group will have better public health outcomes in the next quarter.

H2c. More months of MOUD treatment (regardless of group assignment) in a given quarter will be associated with fewer days of opioid use in the next quarter.

H2d The months of MOUD treatment will mediate the relationship between group assignment and public health outcomes.

Aim 3. The indirect effects of RMC (via treatment and public health outcomes) on public safety outcomes (illegal activity, re-arrest, re-incarceration, and cost-of-crime)

H3a. Relative to the control group, the participants in the two RMC groups will have better public safety outcomes (illegal activity, re-arrest, re-incarceration, and cost-of-crime) in the next quarter.

H3b. Relative to the RMC group, the participants in the RMC-Adaptive group will have better public safety outcomes in the next quarter.

H3c. More months of MOUD treatment and better public health outcomes (regardless of group assignment) in a given quarter will be associated with better public safety outcomes in the next quarter.

H3d The months of MOUD treatment and public health outcomes will mediate the relationship between group assignment and public health outcomes.

Aim 4. The incremental costs and cost-effectiveness of the control vs. RMC vs. RMC-Adaptive in terms of both public health outcomes (days of opioid use, quality adjusted life years (QALYs), cost-of-health-care utilization) and public safety outcomes (re-incarceration and cost-of-crime).

H4a. Relative to the control group over 24 months, the participants in the two RMC groups will have lower cost-per-outcome (e.g., days of opioid reduced; QALYs gained).

H4b. Relative to the RMC group over 24 months, the participants in the RMC-Adaptive group will have a higher cost, but also greater effectiveness in reducing opioid use and in QALYs gained.

H4c. Relative to the control group over 24 months, the participants in the two RMC groups will have significantly lower healthcare utilization, criminal activity, and criminal justice system costs.

H4d. Relative to the RMC group over 24 months, the participants in the RMC-Adaptive group will have significantly lower healthcare utilization, criminal activity, and criminal justice system costs.

Experimental Conditions

(1) Re-Entry as Usual

The type and level of services provided to individuals at re-entry will vary across jails and will be carefully documented. For the most part, individuals released to the community will receive a referral to an OTP, and a subset may potentially be mandated to participate in community based treatment and/or recovery programs such as recovery coaching, and/or sentenced to varying levels of probation. Referrals and services provided to all participants will be documented at each research interview.

(2) Recovery Management Checkups (RMC)

In the RMC condition, participants will have access to services provided as a part of re-entry as usual. In addition, checkups will be provided on a fixed schedule that includes face-to-face monthly checkups for 3 months, and quarterly for the rest of the two years. Participants will have access to referrals and services provided by the jail and MOUD treatment provider as part of their usual re-entry procedures. Individuals will meet with a Linkage Manager (LM) upon study enrollment and during each quarterly checkup, during which they will complete a Brief Treatment Needs Assessment, receive motivational interviewing, linkage assistance, or a check-in on continuing care and recovery support. The priority is to engage the individual into treatment with MOUD as soon as possible at the time of release, however, if individuals express a preference for another form of SUD treatment, the LM will work with that individual to link, engage, and retain them in that form of treatment.

(3) RMC-Adaptive

The RMC and RMC-A conditions differ in three significant ways. First, in the RMC-Adaptive condition, checkups will be provided based on the participant's current need for treatment. In contrast, those in the RMC condition receive checkups on a fixed quarterly schedule regardless of need. The interval between RMC-A check-ups will vary (in one-month increments) depending upon the individual's assessed need for treatment at the prior check-up. Second, in cases where participants have 3 consecutive checkups in which they need treatment, the intervention strategy will be adapted to include a meeting of the LM and treatment staff to determine how to better meet the participant's needs, e.g., a different treatment provider, different type of MOUD or other types of treatment, and/or additional services. Third, if RMC-Adaptive participants are re-incarcerated at the time of their checkup, the LM will meet with the individual while incarcerated to discuss a recovery plan, which may include initiation of MOUD while incarcerated and/or re-linkage to treatment with MOUD upon release.

Instruments, Data Sources, and Measures

Interview data. Baseline participant characteristics, days of MOUD treatment and other SUD treatment received, days of opioid use, symptom counts and health-care-utilization-costs (for Aims 2-3) will come from the 25-minute *Global Appraisal of Individual Needs - Quick (GAIN-Q3)* administered at study enrollment and quarterly for 24 months post-study enrollment. The GAIN-Q3 includes 8 primary domains: 1) background, 2) school problems, 3) work problems, 4) physical health, 5) sources of stress, 6) HIV risk behaviors, 7) substance use, and 8) crime and violence. In each area, there are 5–10 item symptom counts that are correlated ~.9 with the respective 16 to 43 item versions in the full 2-hour GAIN and have 90% sensitivity and 90% specificity for diagnosis from the full GAIN. The response set captures the recency of these symptoms (lifetime, past year, past 90 days, past month) and treatment involvement, then the frequency (days) of behaviors/treatment utilization in the past 90 days. The GAIN-Q3 also includes the behavioral health screener and healthcare-utilization measures recommended by NIH's PhenX common data platform. The GAIN-Q3 includes measures of days of MOUD treatment and other SUD treatment received, and heroin and other opioid use (for Aims 1-2), as well as symptom counts for SUD, other internalizing and externalizing mental health disorders, physical health disorders. It also includes questions on health-care-utilization and costs (for Aim 4).

The interview will be supplemented with the *GAIN-I's Opioid Use Disorder Scale* to give a more specific DSM-5 based symptom count at baseline and each quarter, as well as the General Crime Scale to obtain a more detailed measure of illegal activity and the cost-of-crime (for Aims 2-4). The interview will include questions on quality of life from the *Patient Reported Outcomes Measurement Information System* (PROMIS-R), with U.S. norms to generate quality adjusted life years (QALYs) for Aim 4. QALYs comprise a single metric ranging from 0 to 1, where 0 is equivalent to death and 1 is equivalent to optimal health.

The *Brief Treatment Needs Assessment (BTNA)* will be administered at the beginning of each RMC/RMC-A checkup to facilitate the intervention. It includes sections on a) eligibility for linkage, b) need for treatment (weekly or more frequent substance use since the last assessment, any past month SUD symptoms, or a current self-perceived need for treatment), c) potential barriers to treatment access, and d) motivational readiness for treatment.

Interviews will also document services and activities provided via re-entry as usual, such as: receipt of MOUD received outside of the project-related OTPs and other SUD treatment; assistance with Medicaid; and transportation assistance, referrals, recovery coaching, or case management. Data will be collected via a cloud-based computer program that controls ranges and skip outs and identifies major inconsistencies. All interviews will be taped, and two tapes a month will be randomly selected and reviewed for quality assurance.

Urine Drug Testing

On-site urine screens will be conducted with DrugCheck cups and fentanyl test strip using an immunoassay for rapid (2–5 minutes) qualitative results based on SAMHSA-standard cutoffs for any kind of heroin/morphine/ opioids in general (at 2000 ng/ml), 5 other specific opioids (Buprenorphine, Fentanyl, Heroin/Opioid 2000, Methadone, Oxycodone, Tramadol) and 10 other drugs. Each of these tests has 98%+ accuracy, as well as temperature and validity strips to check for 6 types of adulterants. On-site urine test results will be shared with participants before asking questions about their recent substance use in order to minimize false negatives to 3% or less, as has been done in our prior RMC studies. Dr. Dennis will train the research staff on the protocol and conduct cross-validation of the self-report and urine test data.

Treatment Records Data

Each collaborating OTP will be asked to sign a business associate agreement allowing researchers to extract information from patients' case files on admission dates, treatment received, discharge dates, and discharge status. Each participant will also be asked to sign a release for parallel treatment data from any other MOUD provider or SUD treatment provider from which they receive treatment. Consistent with prior trials and current studies, agencies will provide weekly treatment updates.

Death Records Data

The research team will obtain information from the County Medical Examiner's office when applicable on participants that staff interview logs suggest have died and/or who could not be located for the final follow-up.

Justice Records Data

The study team will abstract information on the charges, admission, and release dates from jail at the time of recruitment through 24 months post-release. In prior studies, measures were largely consistent (kappa = .64) across state and local official records and self-reports, with each source identifying some unique cases of re-arrest or incarceration.

Drug Abuse Treatment Cost Analysis Program (DATCAP)

The cost of standard RMC and RMC-Adaptive will be estimated using the Drug Abuse Treatment Cost Analysis Program (DATCAP), a standardized and widely used costing survey that estimates the direct and opportunity costs of interventions in terms of staff/personnel salaries (plus fringe benefits), other direct costs, value of donated or subsidized resources, and overhead. The DATCAP is designed to facilitate data collection from agency/provider accounting systems and research records. Data are organized in an Excel workbook with built-in algorithms to generate summary statistics using data on intervention engagement and patient case flow: total annual program cost, average annual cost per patient; average cost per treatment episode (per patient).

Measures

The primary outcome measure for the study is Months of MOUD treatment across 24 months post-release for Aims 1 and 4, as well as quarterly for Aims 2 & 3.This is a continuous measure from OTP records (Interclass Correlation Coefficient [ICC]=.37 when measured quarterly). The count will be based on days of medication received (including any take-home dosages), with injectable naltrexone being counted as treatment for 30 days. See section 4.3 for more details on secondary outcomes.

Participants

Inclusion criteria are: meeting the Diagnostic and Statistical Manual version 5 (DSM-5) opioid use disorder (OUD) criteria in the past year, heroin or other opioid use in the 90 days prior to entering jail, and being released from one of the participating jails to the community. Exclusion criteria are: less than age 18, cognitive impairment that precludes ability to give informed consent, and resides outside the service area.

We anticipate that overall, 34% of participants will be female; 11% will be Hispanic; 75% white, 16% black; and 9% mixed/other race. We expect 5% to be ages 18-20, 26% ages 21-25, 48% ages 26-49, and 19% to be 50 to 64, and less than 1% to be age 65 or older. OTPs estimate that about half of patients drop out of treatment within 3 to 12 months.

Opioid Treatment Programs

All OTPs use a clinical assessment to make a diagnosis based on the Diagnostic and Statistical Manual version 5 (DSM-5) placement based on the Patient Placement Criteria version 3, and are licensed by the Illinois Department of Human Services/ Division of Substance Use Prevention and Recovery (SUPR) for the provision of outpatient medication assisted treatment and other SUD treatment services.

Recruitment

Phase I: In Jail Screen for Study Eligibility. The study team will use two methods that have been successfully used in prior studies to recruit eligible individuals from jail settings and to engage them in the study. In the first method, staff at the jail (these may be corrections staff, medical staff, or staff from contracted MOUD providers) will identify individuals who have already been assessed with OUD (as part of the usual screening protocol), provide them with an overview of the study, and, for those interested in learning more about the study, will secure their permission for a study research assistant (RA) to contact the candidate, confirm their eligibility (based on age and residency), and discuss transportation to the research office upon their release. In the second method, the RA will meet with the candidate immediately following their release, briefly overview the study, and discuss transportation to the research office post-release. Both procedures will allow the study team to contact individuals who have initiated treatment with MOUD pre-release as well as those who are quickly released, and may not have initiated treatment with MOUD. The study procedures may vary across the different jail sites dependent upon the established procedures for screening individuals for OUD upon their admission and for engaging them into MOUD prior to their release.

Phase II: Re-entry Meeting, Baseline Data Collection and Randomization. To maximize timely participation in the re-entry meeting, participants will be transported to the research office and given a $45 gift card upon completion of the baseline interview. Using similar procedures in the RMC re-entry trial, from the date of release, 90% were enrolled within 7 days). RAs will then provide a detailed description of the study, and for those who agree to participate, RAs will administer the informed consent, complete the baseline research interview, update the locator, notify the Research Manager to randomize participants, and schedule the next research interview. The Research Manager will randomly assign participants to one of 3 conditions: control, RMC, RMC-A. Urn randomization adjusts the probability of assignment to each condition in ways that simultaneously minimizes differences in multiple stratification variables. The base rate will be set at 33% to each condition, and software set to simultaneously balance assignment by the county, days of opioid use in the 90 days prior to incarceration, and probation status at the time of release. It will also take into account participant characteristics that have been previously associated with differences in MOUD treatment retention and outcomes, including sex, age, cocaine use, and mental health problem severity. The Research Manager will enter the information into the program, generate the assignment, and inform the participant's RA of the assignment. Next, persons assigned to the RMC or RMC-A conditions will meet with a linkage manager.

Quarterly Research Interviews

RAs will complete 90-minute enrollment and quarterly follow-up research interviews with participants in all conditions. Study participants will receive a $45 gift card - $35/interview and $10/urine. The team will implement Dr. Scott's structured follow-up model which has reliably produced over 90% follow-up rates across studies involving over 70,000 patients regardless of population, primary drug type including heroin, and over follow-up periods ranging from 3 months to 18 years. Steps include: (a) contacting participants within 24-48 hours of study enrollment to collect additional locator information and mailing a schedule card for the next interview, (b) tracking status of interviews and locator information in a secure database, (c) assigning each case to a follow-up case tracker, (d) verifying locator data, (e) conducting outreach for unverified cases and discussing them at weekly meetings, (f) mailing thank-you cards to participants and collaterals, (g) scheduling follow-up appointments in advance, (h) mailing 3 and 6 week post-enrollment flyers, (i) implementing returned-mail procedures, (j) calling participants 6 weeks before appointment to confirm date and location (phone vs. research office), (k) conducting outreach for unconfirmed cases and reviewing them at weekly meetings, (l) completing follow-up interviews and scheduling next appointments, (m) implementing a no-show protocol, and (n) incentives for both completing the interview and urine drug test. Progress will be monitored with daily management reports.

Analytic Plans and Statistical Power

Missing data

Participants will complete their enrollment interviews prior to randomization. Based on prior studies conducted by the applicants, it is expected that approximately 90% or more of the 10 post-enrollment interviews will be completed. Among these completed interviews, prior studies indicate that there will be less than 1% additional missing data on any of the core items required to test the hypotheses. "Item-level" missing data will be replaced within subject where possible, or with multiple imputations or restricted maximum likelihood to provide the least biased estimate for each analysis. To further reduce potential bias, analyses will be rechecked by running them without missing data. If there are any clinically significant differences ($d>|.2|$), a general latent variable framework will be used to analyze non-ignorable or systematic missing data that tests whether missing data is qualitatively different by condition. "Observation level" missing data from when an interview was not conducted will be evaluated in an intent-to-treat analysis using the average of the available observations or the last observation.

<u>Analysis of Comparative Effects (Aim 1)</u>

The analysis for Aim 1 is designed to evaluate, (H1a) relative to the re-entry as usual control group, the extent to which providing RMC and RMC-Adaptive significantly increases the rates of initiating treatment with MOUD and months of MOUD treatment over 24 months, and (H2a) these same outcomes for RMC-Adaptive relative to RMC. The marginal effects will be initially evaluated with a Chi-square (for MOUD treatment initiation) and Mann Whitney U rank test of the distributions (for months of MOUD treatment) comparing the main effect. Duration of MOUD treatment ranges from 0 to 24 months but is expected to be zero saturated, right skewed and multimodal with concentrations at none (no initiation), 1-3 months (first half to drop out) and then another distribution between 3 and 24 months (longer term patients). Mann-Whitney U tests address these issues by ranking observations (regardless of condition) and then comparing conditions on the distributions of the ranks. For non-normal distributions it is more powerful than a t-test. The proposed samples are sufficiently large that U will approximate a normal distribution and can be transformed into a z-score and/or Cohen's effect size d.

Because the size of the RMC effects increase with repeated intervention exposure, we will evaluate the changes in the observed effects on months of MOUD treatment over time using multilevel structural equation modeling (MSEM) with mixed effects in MPlus (version 6.1) controlling for the number of months (i.e., % of months of participation). The analysis will model observations (Level 1) nested within participants (Level 2), and participants nested within counties (Level 3). Random assignment to 1 of 3 groups, being released on probation and being mandated to treatment will each be modeled as a Level 2 predictor. We will test differences in the a-intercept and slope over time. Participants will be modeled as a random factor to control for repeated observations on the same person. Because probation status and type of medication received may change over 24 months, these are represented as time-varying covariates by observation (Level 1). The impact of dosage is evaluated with growth curve analysis to see if the difference between RMC-A and the control group increases with checkup dosage (i.e., by observation at level 1). As a function of ICC, these kinds of repeated measures analyses in general increase the effective number of n for the analysis to somewhere between the number of unique individuals (n=750; when ICC=1) and the number of observations (o=6750; when ICC=0). MSEM also incorporates measurement error corrections.

Analysis of Indirect Effects on public health outcomes (days of opioid use, OUD symptoms, quality of life, and the cost-of-health-care utilization) (Aim 2)

The first part of the analysis for Aim 2 is designed to evaluate H2a relative to community re-entry as usual control group. It will examine the extent to which providing RMC and RMC-Adaptive in one quarter significantly improve public health outcomes in the next quarter, and H2b, relative to RMC, to determine if RMC-Adaptive further improves public health outcomes in the next quarter. It will parallel the analysis for Aim 1. The second part of the analysis for Aim 2 is to examine the extent to which the months of MOUD treatment in the prior quarter mediates these two relationships H2c and H2d respectively, as shown in Figure 3. Evaluation across two quarters also serves to establish temporal order, and strengthen our ability to make causal inferences. Modeling the effects of MOUD treatment is important as even the re-entry as usual control group will have some level of it, and to the extent they do, it is included in this effect. We will test these correlations and then use them to separate the direct and indirect effects of the experimental intervention on each outcome using MSEM. To do so, we will arrange records in a hyper-vertical file with each record having data from a given quarter and the next available quarter as we have done before in prior studies. We will control for repeated observations by including person as a random effect, and include the duration between observations to partial out any methods effects. This suggests the likelihood of an indirect effect via MOUD treatment. Note that at the time, other types of MOUD had not yet become widely used. Indirect effects of the experimental intervention on each outcome will be evaluated using MacKinnon's joint-significance testing of the path z-scores with a Sobel test using a standard error based on bootstrapping and criteria of $p<.05$ on the degree of difference between conditions. We will also examine the effects of pre-release treatment with MOUD, type of MOUD, county, checkup dosage, and sex by testing whether the observed SEM paths are 'invariant' across each.

Analysis of Indirect Effects of RMC (via treatment and public health outcomes) on public safety outcomes (illegal activity, re-arrest, re-incarceration, and cost-of crime) (Aim 3)

The analysis for Aim 3 is designed to evaluate: (H3a) relative to community re-entry as usual, the extent to which providing RMC and RMC-Adaptive in a given quarter significantly improves public safety outcomes in the next quarter; and (H3b) relative to RMC, whether RMC-A in a given quarter improves public safety outcomes in the next quarter. It will parallel the analysis for

Aims 1 & 2. The second part of the analysis for Aim 3 is to examine the extent to which the months of MOUD treatment and public health outcomes in the prior quarter mediates these two relationships (H3c and H3d), respectively, as shown in Figure 3. We will test these relationships in a manner similar to the analysis for Aim 2, but here we will allow all three of the opioid predictors to enter the model and examine their ability to predict the other outcomes together in a MSEM. Data from these analyses will be combined into a path model, and the indirect effects of the experimental intervention on longer-term outcomes will be evaluated using MacKinnon's joint-significance testing of the path z-scores with a Sobel test using a standard error based on bootstrapping and criteria of $p<.05$ on the degree of difference between conditions.

Cost-Effectiveness Analysis (Aim 4)

The Cost-Effectiveness Analysis (CEA) will be framed from the healthcare sector (e.g., OTP provider, third party payers) and societal (i.e., factoring in costs of criminal activity and criminal justice events) perspectives. For each site, differences in costs and effects between study conditions will be estimated using multilevel general linear models (e.g., generalized linear mixed models or GLMM). These models can control for factors that are unbalanced between study arms and allow for the inclusion of random effects that can account for clustering at the site-level as well as the individual (client) level. With GLMM, the most appropriate mean and variance functions can be selected based on the fit of the data. Predicted mean effectiveness and mean costs of the RMC interventions and control are compared and used to calculate incremental cost-effectiveness ratios (ICERs), the main result for Aim 4. The ICER reports the marginal cost to achieve a unit of desired outcome (e.g., a QALY or one fewer overdose) in an RMC strategy relative to control (or in RMC-Adaptive relative to RMC). ICERs must be interpreted according to the value society places on this "per unit" improvement or reduction. Such a value is known as willingness-to-pay (WTP) and is used to designate the cost-effectiveness threshold. Although it is not intelligible exactly what society is willing to pay for one less overdose or other outcome, the analyst can project a value or range of values for WTP per unit of outcome to interpret the ICER in terms of net benefit (NB) and incremental net benefit (INB). For instance, if society values one fewer opioid overdose at $1,000, the NB of each study condition is the number of avoided overdoses over follow-up multiplied by 1,000, minus condition costs. The INB is simply the difference in NB between study conditions. The proposed analyses will use a nonparametric bootstrapping method within the multivariable framework to compute confidence intervals for assessing uncertainty in the ICERS for RMC-Adaptive versus control, RMC versus control, and RMC-Adaptive versus RMC. These confidence intervals form cost-effectiveness acceptability curves (CEACs) based on what society may be willing to pay to achieve an additional unit of effect (e.g., one day of abstinence or one QALY). Given that commonly accepted value thresholds do not exist for most outcomes, the CEACs provide context for interpreting the CEA results by illustrating the probability that a strategy is a good value for different value thresholds. For instance, in the context of RMC-Adaptive versus control, the ICER reports the marginal cost of achieving one percentage point reduction in overdose for individuals receiving RMC-Adaptive relative to controls. The calculation of the ICER can be modified such that the numerator, incremental costs, includes any savings generated by reductions in healthcare or criminal justice costs.

Interventions

(1) Re-entry as usual

The types and levels of community services provided individuals at re-entry will vary across jails. For the most part, upon their release to the community, individuals who have been diagnosed with opioid use disorders will receive a referral from the jail or their OTP to a local

OTP that includes the location, date, and time of their next treatment appointment. Referrals and services provided to all participants related to their treatment for opioid use disorders will be documented at each research interview.

(2) Recovery Management Check-up (RMC)
In the RMC condition, participants will have access to referrals and services provided by the jail as part of their usual re-entry procedures. In addition, RMC checkups will be provided on a fixed schedule that includes face-to-face monthly checkups for 3 months and quarterly checkups for the remainder of the two-year intervention period. The priority will be to engage the individual into treatment with MOUD as soon as possible at the time of their release to the community. However, if individuals decline to participate in treatment with MOUD, but express an interest in another form of substance use disorder (SUD) treatment, they will receive the standard linkage and referral components of the RMC to their preferred form of treatment. Individuals will meet with a Linkage Manager (LM) at each quarterly checkup, during which they will complete a *Brief Treatment Needs Assessment*, receive motivational interviewing and recovery support, and linkage or re-linkage to treatment, if needed.

(3) RMC-Adaptive (RMC-A)
In the RMC-A condition, participants will have access to referrals and services provided by the jail as part of their usual re-entry procedures. The RMC-A condition differs in 3 ways from the standard RMC. First, participants will receive monthly checkups during the first 2 months post-release with additional checkups dependent upon the participant's progress. The interval between RMC-A check-ups will be adjusted (in monthly increments) based on the individual's status at the prior check-up. Second, after 3 consecutive checkups in which the individual has an assessed need for treatment, the LM will meet with treatment staff to determine if changes to the treatment plan or additional support are needed. Third, if an RMC-A participant is re-incarcerated at the time of their checkup, the LM will meet with the individual in the jail to discuss a recovery plan, re-linkage to treatment, and transportation to the research office upon release.

4.3 Outcome measures

Name	Type	Time Frame	Brief Description
Months of MOUD treatment	Primary	Across 24 months post release for Aim 1 and 4; quarterly for Aims 2 & 3	A continuous measure from OTP records (Interclass Correlation Coefficient [ICC] =.37 when measured quarterly). The count will be based on days of medication received (including any take-home dosages); injectable naltrexone will be counted as treatment for 30 days. Missing records data will be estimated from self-report.
Opioid Use Disorder (OUD) service cascade	Secondary	Across 24 months post-release for Aim 1	Calculated from justice and treatment records, these will include both dichotomous measures of whether each of the following events happen and continuous measures of the days from jail release to: a) initiation of treatment with MOUD, b) engagement in MOUD treatment for at least 6 weeks, c) retention in MOUD treatment for at least 90 days (median in national data), and d) retention for at least 6 months, as well as

			times from post-drop out and relapse to re-linkage to treatment with MOUD. Largely used descriptively.
Days of Opioid Use	Secondary	Quarterly for Aims 2 and 3; across 24 months for Aim 4	A self-reported count 0 to 90 days of using any kind of opioids each quarter (test-retest rho=.95; ICC=.34 across quarters). There will also be additional measures of the days of using heroin, fentanyl, and prescription opioid misuse for descriptive use. All come from a standardized assessment tool called the *Global Appraisal of Individual Needs* (GAIN).
Opioid Use Disorder (OUD) Symptoms	Secondary	Quarterly for Aims 2 and 3; across 24 months for Aim 4	A self-reported count of the 0 to 11 the *Diagnostic and Statistical Manual version 5* (DSM-5) symptoms of Opioid Use Disorders (OUD) each quarter from the GAIN (alpha=.95; ICC=.28 across quarters). There will also be alternative measures for OUD symptoms in the past month, year, and lifetime, as well as a measure of DSM-5 symptoms across other SUD each quarter.
Quality of Life (QoL)	Secondary	Quarterly for Aims 2 and 3; across 24 months for Aim 4	This measure is based on the *Patient Reported Outcomes Measurement Information System* (PROMIS) – R. It is the self-reported frequency of problems in with reference to the past 7 days in 8 domains: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and cognitive function ability, and an overall measure of pain intensity.
Costs-of-Healthcare-Utilization	Secondary	Quarterly for Aims 2 and 3; across 24 months for Aim 4	This cost measure is based on the self-reported frequency of healthcare services related to substance use, mental health, and physical health, measured in units such as “days,” “visits,” or “episodes”, which are multiplied by corresponding monetary conversion factors (price weights for a unit of service) to estimate a continuous “total healthcare costs” variable and trimmed at the 99% percentile due to sharp right skews (ICC=.27 across quarters). We will collaborate with the JCOIN economic studies across hubs on the measures to be used for this variable. Dr. McCollister and her colleagues updated these cost estimates to 2017 and will adjust them forward using the consumer price index.
Illegal Activity	Secondary	Quarterly for Aims 3; across	This is a self-reported count of 19 items across different types of illegal activities

		24 months for Aim 4	related to property crimes (e.g., vandalism, bad checks, theft, breaking and entering), personal crime (e.g., assault, rape, murder), and substance use (driving under the influence, distribution, prostitution, gang membership, gambling) in the past quarter (alpha=.9; ICC=.20 across quarters). An alternative version collects the frequency of each crime above. Another alternative is a shorter 5-item score of the average of proportional items (divided by their range) for the recency and days (during the past 90) of illegal activity and of supporting oneself financially with illegal activity. These self-report questions come from the GAIN.
Re-arrest and Re-incarceration	Secondary	Quarterly for Aim 3; across 24 months for Aim 4	A dichotomous measure of whether the person has been re-arrested and/or re-incarcerated, as well as the associated charges for descriptive purposes (ICC=.35). Also alternative measures of the days to each event and the number of events. All measure are both within and across quarters.
Costs-of-Crime	Secondary	Quarterly for Aim 3; across 24 months for Aim 4	This cost measure is based on the self-reported frequency of 12 criminal offenses times their respective societal cost per offense based on the most recent economic estimate, which will be used to estimate a continuous "total cost-of-crime" variable in whole dollars and trimmed at the 99% percentile due to sharp right skews (ICC=.03). We will collaborate with the JCOIN economic studies across hubs on the measures to be used for this variable. Dr. McCollister and her colleagues updated these cost estimates to 2017 and will adjust them forward using the consumer price index.
Quality Adjusted Life Years (QALYs)	Secondary	Across 24 months post release for Aim 4	This measure is based on the *Patient Reported Outcomes Measurement Information System* (PROMIS) – R. It is the self-reported frequency of problems in with reference to the past 7 days in 8 domains: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and cognitive function ability, and an overall measure of pain intensity. QALY (0-100%) times 0.25 years for each quarter and summed across 8 quarters/24 months post-release. While missing data will

			be imputed, from a point of death on will be treated as 0. In addition to being compared between groups, data can be scaled to U.S. norms using the AHSR data.

4.4 Statistical Design and Power

Primary Outcome. Based on the proposed design and data presented earlier, this power analysis for the primary variable, "Months of MOUD treatment," is based on the assumptions that:

1) 750 adults with OUD who are released from the 6 county jails can be recruited
2) Participants will be randomized to 3 conditions (250 per group)
3) Data will be collected at enrollment and 8 follow-up observations (at 3, 6, 9, 12, 15, 18, 21, and 24 months post enrollment) and combined with continuous records data to create an observation for every person
4) H1a will have unequal sample sizes (250 control vs. 500 for RMC+RMC-adaptive)
5) H1b will have equal sample sizes (250 RMC vs. 250 RMC-Adaptive)
6) The range of effect sizes in prior experimental studies of RMC (without focusing on MOUD treatment) was 0.21 to 0.50.

Under these assumptions, there is over 99% power with two-tailed alpha of .05 to detect a Cohen's effect size d of 0.35 or more for H1a and 0.40 or more for H1b. There is over 80% power to detect effect sizes of d=0.22 and 0.25 respectively. Use of multi-level modeling, multiple sources of data, and baseline covariates should further improve power and/or allow the detection of smaller effects. The effects of RMC and RMC-Adaptive on the months of MOUD treatment will be initially evaluated with a Mann Whitney U test of the distributions comparing the main effect of Re-entry as Usual vs. RMC. This Mann-Whitney U test is proposed as a conservative test in case the variables have a non-normal and potentially bimodal distributions (e.g., zero saturation or a small group with perfect retention or 24 months). The proposed samples are sufficiently large that U will approximate a normal distribution and can be transformed into a z-score and/or Cohen's effect size d.

For the power analysis of later hypotheses, we also assumed that:

1) Data will be available for at least 90% of each of the follow-up observations (225 per group at follow-up and 2050 observations per group based on enrollment plus 90% of 8 quarterly follow-up waves)
2) The inter-item correlation (ICC) across repeated observations will range from 0.03 (cost-of-crime) to .37 (quality of life) with the later reducing the effective observations to 1694 to 571 respectively)
3) There will again be unequal number of observations when comparing control (1694 to 571) vs. RMC+RMC-Adaptive (3388 to 1142), and when comparing RMC (1694 to 571) and RMC-Adaptive (1694 to 571).

We have over 99% power to detect an effect size of 0.22 or more and 0.25 respectively for the smallest sample size. It has over 80% power to detect an effect size of 0.16 or more for both. The variable (or a transformed version of it) will then be analyzed in a multilevel structural equation model (MSEM). For Aim 4, the power follows what is presented above for Aim 1.

The table below summarizes the number of participants/observations, expected effect size, estimated power, and proposed statistical method for each of the primary and secondary

outcome measures. Sample sizes below are per group. Power given below is for the RMC vs. RMC-A comparison – the control vs RMC+RMC-A will always have more n and power.

Primary*and Secondary Outcome Measure	**Number of Participants & Observations Per Group (from Survey Observations and records if **)**	**Expected Effect size**	**Estimated Power**	**Statistical Method**
Months of Treatment Participation with MOUD for H1a & H1b (*Primary)	250 Participants per group (Combined over observations) **	Cohen's d=.4 or more	99% power or more	Mann Whitney U (MWU) test of the distributions comparing the main effect of groups
Opioid Use Disorder (OUD) Service Cascade for H1a & H1b*	250 Participants per group (Combined over observations) **	Odds Ratio=1.5	90% or more	Odds Ratio of random assignment controlling for site and other urn randomization variables
Days of Opioid Use for H2a-d, H4a & H4b (ICC=.34)	250 Participants with 607 effective observations per group	Cohen's d or path coefficient of 0.2 or more	90% or more	MWU test as above and Multilevel structural equation modeling (MSEM) with mixed effects in MPlus (version 8). The analysis will model observations (Level 1) nested within participants (Level 2), with participants modeled as a random factor. Random assignment to the 2 groups will be modeled as a Level 2 predictor. We will test differences in the a-intercept and slope over time. \
Opioid Use Disorder (OUD) Symptoms for H2a-d (ICC=.28)	250 Participants with 693 effective observations per group	Cohen's d or path coefficient of 0.2 or more	90% or more	MWU and MSEM – same as above
Quality of Life (QoL) for H2a-d, H4a & H4b (ICC=.37)	250 Participants with 394 effective observations per group	Cohen's d or path coefficient of 0.2 or more	80% or more	MWU and MSEM – same as above
Costs-of-Healthcare-Utilization for H2a-d, H4a & H4b (ICC=.27)	250 Participants with 709 effective observations per group	Cohen's d or path coefficient of 0.2 or more	95% or more	MWU and MSEM – same as above
Illegal Activity for H3a-d (ICC=.20)	250 Participants with 854 effective observations per group	Cohen's d or path coefficient of 0.2 or more	99% or more	MWU and MSEM – same as above
Re-arrest and Re-incarceration H3a-d, H4c & H4d (ICC=.35)	250 Participants with 594 effective observations per group	Cohen's d or path coefficient of 0.2 or more	90% or more	MWU and MSEM – same as above

Costs-of-Crime H3a-d, H4c & H4d (ICC=.03)	250 Participants with 1694 effective observations per group	Cohen's d or path coefficient of 0.2 or more	99% or more	MWU and MSEM – same as above
Quality Adjusted Life Years (QALYs) for H4a & H4b	250 Participants per group (combined over observations)	Cohen's d or path coefficient of 0.2 or more	90% or more	MWU and MSEM – same as above

4.5. Subject participation duration: 24 months

4.6. FDA-regulated intervention

This study meets the criteria for Investigational New Drug exemption status for the following reasons:

a. Burprenorphonine with or without naloxone (including Suboxone®, Subutex®, Zubsolv®, Bunavail®, Butrans®, Buprenex®, Probuphine®, and Belbuca®), methadone (including Methadose®, Dolophine®, Diskets®, and Methadone Intensol®), and naltrexone (including Vivitrol®, ReVia®, Adepend®, Depade®, Nalorex®, and Trexan®) are each FDA-approved medications for treating OUD that are lawfully marketed in the United States;
b. The study is not intended to be reported to FDA in support of new indications or to support any other significant changes in the labeling of the drugs, nor to support significant changes in advertising for the drugs; and
c. The study does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drugs.
d. MOUD will only be provided in the context of regular care by organizations and staff already licensed to do so by the state.

4.7 Dissemination Plan

The Principal Investigator (Scott) and all Co-Investigators ensure the following:

- We will provide requested data to the CTC and MAARC in a timely fashion in accordance with the policies and procedures established in study protocols and by the SC. In addition, we will provide NIDA with access to all data generated under this award, subject to rules specified in our Certificates of Confidentiality. We will also share our data upon request with the SC and subcommittees reporting to the SC when appropriate
- JCOIN is intended to be a national resource, and as such, and as one of the Clinical Research Center we will share our data under provisions that safeguard the privacy and confidentiality of respondents.
- We will cooperate to ensure the timely and broad dissemination of lessons learned, to inform researchers and health care systems engaged in research and beyond.
- We will work closely with NIDA, the Coordination and Translation Center, the Methodology and Advanced Analytics Resource Center, and Steering Committee members to disseminate findings and products from our work.
- Qualified members of our team will actively participate in a wide variety of network activities designed to facilitate dissemination, including, but not limited to: providing mentorship to participants in the Coordination and Translation Center Research Education Core,

participating in reviews of network publications, actively engaging in harmonization activities, making data from their study available to others, serving as a reviewer for Coordination and Translation Center Rapid Response and Pilot Research Project proposals.

- The study will be registered and the results stemming from this study will be submitted to ClinicalTrials.gov as outlined in the policy and according to the specific timelines stated in the policy;
- All informed consent documents for the study will include a specific statement relating to posting of clinical trial information at ClinicalTrials.gov; and
- Chestnut Health Systems, the recipient institution, has an internal policy in place to ensure that clinical trials registration and results reporting occur in compliance with policy requirements.

In addition to the above, as the investigators have consistently done in their prior clinical trials studies, findings from this study will be widely disseminated in several ways. These include:

- Presentations at scholarly and research-oriented conferences, such as the College on Problems of Drug Dependence (CPDD), Addiction Health Services Research (AHSR), American Public Health Association (APHA), and American Psychological Association (APA);
- Publications in peer-reviewed journals in the areas of opioid treatment, opioid treatment programs, and overdose prevention, such as Addiction, Drug and Alcohol Dependence, Journal of Substance Abuse Treatment, JAMA – Psychiatry and JAMA Internal Medicine; public health and health policy, such as the American Journal of Public Health, American Journal of Preventive Medicine, Health Affairs, Chronic Disease Prevention; and health services research, such as Health Services Research and Journal of Behavioral Health Services Research;
- Presentations for policy makers, treatment and prevention providers, such as meetings of the National Association of State Alcohol and Drug Abuse Directors (NASADAD), the American Association for the Treatment of Opioid Dependence (AATOD), and relevant meetings sponsored by the Centers for Disease Control and Prevention (CDC) and the Substance Abuse and Mental Health Services Administration (SAMHSA).