

**Data and Safety Monitoring Plan (DSMP) for the  
Recovery Initiation and Management after Overdose (RIMO) Experiment**

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*Below is the data safety monitoring plan outlined per the National Institute of Drug Abuse's (NIDA's) checklist at <https://www.drugabuse.gov/funding/clinical-research/guidelines-developing-data-safety-monitoring-plan/guidelines-developing-data-safety-monitoring-pl-2>*

**SUMMARY OF THE PROTOCOL**

**1. Brief description of the protocol, procedures, and table for schedule of events**

This study targets individuals in Chicago who have received naloxone administered by first responders within the past week to reverse an overdose, but who have not entered into MAT. Study participants will be recruited through partnerships with the Chicago Fire Department (CFD) and/or Police Department (CPD); first responders will be trained to seek consent from individuals who are alert and oriented after receiving naloxone for future contacts by research staff as part of the naloxone standard protocol. Those who consent will be contacted and screened for study eligibility ideally within one week of naloxone administration; eligible participants will be randomly assigned either to the control group, i.e., referral to MAT as usual, or to Recovery Initiation and Management after Overdose (RIMO), an assertive linkage and recovery support intervention. This intervention builds on an evidence-based intervention for treatment linkage, monitoring, and recovery support evaluated in 3 prior clinical trials by the study team.

In Phase 1 (R21), the study team worked with the CFD to train Emergency Medical Service (EMS) teams to obtain authorization for release of contact information from individuals after an overdose reversal. The experimental pilot study tested the feasibility of each step in the intervention protocol and compared individuals who were randomly assigned to receive either a treatment referral pamphlet or the RIMO intervention on treatment received at 30-day follow-up. Qualitative data was also obtained from a focus group with participants in the RIMO group. A total of 75 individuals who had received naloxone from EMS were informed about the study; 50 (67%) of these signed the authorization form and provided their contact information; 33 met with the study team, consented to participate, and were randomized. Compared to the control group, the RIMO group (n=16) had higher odds of receiving any treatment for opioid use (OD = 7.94) and any MAT (OR = 20.2); they received significantly more days of opioid treatment (15.2 vs. 3.4) and more days of MAT (11.2 vs. 0.76) relative to the control group (n=17; all p < .05). Qualitative data highlighted the core components of the RIMO intervention. The pilot study demonstrates the feasibility of partnering with EMS and using the RIMO intervention to address the challenges of linking and engaging individuals into MAT after opioid overdose. These findings have been submitted for publication (Scott et al., under review) and were used to refine the study design for phase 2.

In Phase 2 (R33), research staff will continue to work with the CFD's EMS division and CPD to identify people who have just had an opioid overdose reversed with naloxone, recruit them into the trial, randomize them to a passive referral (via a brochure) vs. the RIMO experimental group. Using the study recruitment and RIMO procedures refined in Phase 1, a total of 350 individuals will be recruited and randomly assigned to the "referral to MAT" control or to "RIMO". All participants will receive standardized assessments at baseline and 3, 6, and 9 months post-randomization. The study's aims and their associated hypotheses are:

**Aim 1: Evaluate RIMO's direct effect on linkage to MAT, length of time on MAT, dropout, and total days of MAT.**

H1: Relative to the control group, RIMO will have a direct effect on: a) initiating MAT sooner, b) staying on medication longer, c) reducing dropout, and d) receiving more total days of MAT.

**Aim 2: Evaluate RIMO's direct and indirect (via MAT) effects on time to relapse, opioid use, and opioid-related overdose.**

H2: RIMO will have direct and indirect (via days of MAT treatment) effects on: a) time to relapse, b) days of opioid use, and c) number of overdoses.

**Aim 3: RIMO's direct and indirect (via MAT and opioid use) effects on opioid-related fatalities, OUD symptoms, physical health, mental health and the cost of health care utilization.**

H3: RIMO will have direct and indirect (via days of MAT treatment and days of opioid use) effects on: a) opioid-related fatalities, b) opioid use disorders symptoms, c) physical health, d) mental health, and e) cost of health care utilization.

Referral Only Control. During the phase 1 pilot, we collaborated with our study partners as well as the Illinois Opioid STR partners to develop a brochure that includes a list of MAT providers in Chicago, and their location, telephone number, hours of operation, adjacent bus lines, and type of funding accepted (e.g., Medicaid). In addition, the brochure includes a range of other SUD treatment options (e.g., residential or outpatient drug-free treatment), including office-based physicians who prescribe buprenorphine or other forms of MAT. This brochure is will be given to participants in both groups at the baseline assessment. Research staff will follow a script that does not include any statements regarding motivation for treatment. At present, based on our interviews with key informants and focus group with pilot study participants, there is currently no systematic method in place for referring individuals to MAT (or other SUD treatment) either from the first responders following administration of naloxone or at the EDs following their admission for opioid-related overdose. Hence, this condition represents more than the “usual care” in the community.

Recovery Intervention and Management after Overdose (RIMO) is a version of Recovery Management Checkups (RMC) that has proven effective in 3 prior clinical trials, a quasi-experiment, and now in the randomly controlled pilot in RIMO's phase 1. For those assigned to the RIMO group, the Linkage Managers (LM) will use motivational interviewing (MI) techniques to: 1) identify the need for treatment and barriers to going, 2) discuss with patients the benefits of their decision to go to treatment, including activities they might enjoy as well as things they do not like about their alcohol/substance use, 3) provide personalized feedback to participants about the status of their condition based on responses to the assessment instruments, 4) help participants resolve ambivalence about their use and move them toward a commitment to change by accessing additional care, 5) address existing barriers to treatment (e.g., childcare, transportation), 6) schedule a treatment appointment, and 7) facilitate SUD treatment re-entry and engagement. The LM will stay in contact with the patient weekly by telephone for at least 4 weeks to ensure that patients both initiate and remain engaged in SUD treatment. This includes working with the individual and the treatment provider to minimize early discharges. Specifically, the Linkage Manager will follow-up with the treatment agency and/or the patient to see if the patient showed for the appointment. For participants who miss a dose, the LM will contact them to discuss barriers and ways to remove them. Additionally, the LM and MAT provider will coordinate information on the participant's barriers to treatment engagement (i.e., scheduling, transportation) and assist the participant in problem-solving solutions to support their treatment retention. During the first 30 days of MAT, the research team will provide transportation assistance for those in need.

For participants who refuse the referral to MAT, the LM will use motivational interviewing (MI) techniques to explore the perceived benefits and consequences of the individual's current opioid/heroin use as well as explore their motivation for treatment. Using empathy and reflection, the LM will explore the issues and barriers participants face when thinking about going to treatment. Using open-ended questions, the LM will explore not only reasons the individual opted out of the referral to MAT, but also the potential benefits of treatment. The LM will try to develop some discrepancy between where the participant is currently and where they want to be. The LM will use the MI technique of “rolling with resistance” and assure the participant that the decision is up to him/her regarding treatment - empowering the participant in the decision process and encouraging “change talk”. The LM will document the various reasons that participants cite for declining the treatment referral. Learning more about the reasons for these refusals can further inform the development or refinement of strategies for improving linkages. Our experience with other similar trials indicates that many refusals are situational or temporary in nature (e.g., illness, fatigue, sick family member) and simply re-contacting the person at a later date is, in some cases, sufficient to convert a refusal. We will routinely re-contact individuals who refuse linkage to detox or MAT to ascertain if their feelings about entering treatment have changed and continue to engage with them using MI. If the individual is not interested in MAT or other types of treatment, the LM and participant will develop an alternative action plan, which may include specific behaviors and recovery activities (e.g., carry naloxone, attend self-help, get a sponsor) to reduce or stop use.

Follow-up. The team will implement Dr. Scott's follow-up procedures and conduct assessments at 3, 6, and 9 months post-randomization. This model has reliably produced over 90% follow-up rates across studies involving over 70,000 participants of diverse characteristics over follow-up periods ranging from 3 months to 19 years. Steps include: (a) contacting all participants within 24-48 hours of study intake to collect additional locator information and mailing a schedule card for the next interview, (b) recording information in an MIS, (c) assigning each case to an experienced 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, (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, and (m) implementing a no-show protocol. Participants will receive a \$25 incentive upon completion of each interview (\$100 across). Progress will be monitored with daily management reports. These procedures will help maintain participant contact for individuals in both the RIMO and referral-only groups.

**Data Editing and Quality Assurance.** When possible, computer-assisted personal interviews will be conducted. The GAIN interview conducts range checks, makes simple and complex skips, and allows immediate consistency checks. If an interview needs to be done with paper and pencil (e.g., detention, jail, and hospital), the interviewer will field edit it followed by a second edit to verify that key fields are complete, provide feedback and/or get clarification of questions, and mark any missing/bad data. The Research Manager will review inconsistent or missing data with the interviewers. When the data are keyed, the computer system will again check for range and consistency across multiple items. Weekly management reports will be used to monitor performance and error reports will be reviewed weekly until there are no major problems (or when there is a new staff person), then monthly thereafter.

**Missing data.** Participants will complete their baseline interview prior to randomization. Based on prior studies conducted by the applicants, it is expected that approximately 90% or more of the 3, 6, and 9-month post-randomization interviews will be completed. Among these completed interviews, prior studies conducted by the team indicate that less than 1% will have additional missing data on any of the core items required to test the study hypotheses. Multiple imputations will be used to replace the small amounts of missing data to allow 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.

Table 1.1 provides a schedule of events by person. We are currently planning to start recruitment immediately and for 18 to 24 months. Follow up (and RIMO) at 3, 6, and 9 months will start at month 3 and be completed between months 30 to 36 depending on how long it takes to recruit the sample. Quality assurance checks will be done until all staff are certified and then quarterly during the study. Annual data safety monitoring reports will be done annual (discussed further below) and then main findings will be started immediately upon the completion of data collection.

	<b>Timing</b>	<b>Passive Referral Control</b>	<b>RIMO Experimental</b>
Screening and recruitment after overdose	Up to 1 week prior to random assignment	Yes	Yes
Informed Consent and Randomization	Point of random assignment	Yes	Yes
Provide a brochure on accessing MAT and financial assistance	Point of random assignment,	Yes	Yes
Interview, urine test and record abstraction	Enrollment, 3, 6, and 9 months post enrollment	Yes	Yes
RIMO Linkage Assistance	Enrollment, 3, 6, and 9 months post enrollment	--	Yes

## **2. Primary and secondary objectives and outcome measures**

The primary outcome measure for the study is the GAIN-Quick Version 3 (GAIN-Q3). The GAIN-Q3 includes 4-6 symptom count screeners that are correlated .9 or more with the 11 to 43-symptom version in the full GAIN. It also has cut points with excellent (~90%) sensitivity, specificity, and area under the curve (AUC) relative to the full GAIN in 9 problem areas related to substance use disorders, physical health, internalizing and externalizing mental health disorders, as well as school, work, stress, HIV risk behaviors/victimization, and crime/violence. The days of use measures have been validated against the Timeline Follow-back, collateral reports, and urine and saliva tests. The GAIN-Q3 also includes summary measures for health care utilization, functional impairment, quality of life, and life satisfaction. The GAIN-Q3 includes the behavioral health screener and health care utilization measures that have been recommended by NIH's Phenx common data elements as two of the most reliable, valid, efficient, and inexpensive tools in the field. At each follow-up, the Q3 follow-up will be supplemented with a) a section on overdose and naloxone experiences, and b)

symptom counts from the OUD scale. Table 2.1 crosswalks the key independent measures and secondary outcomes from the hypotheses to their definitions, reliability, data sources, and the specific aims they address.

<b>Table 2.1. Crosswalk of Variables, Definition, and Aims</b>	H1	H2	H3
<b>Experimental Assignment:</b> Based on computer-generated urn randomization, participants will be assigned to the referral only control group or the experimental RIMO condition.	R	R	R
<b>MAT Time to Initiation:</b> Days from index naloxone administration to the initiation of any kind of MAT, from treatment records.	O		
<b>Length of Staying on Medication:</b> Days between MAT initiation and discharge, from treatment records.	O		
<b>MAT Days:</b> Total days of MAT over 9 months from GAIN-Q3 and treatment records.	O	M	M
<b>Time to Relapse:</b> Days from randomization to next subsequent use of opioids or heroin based on GAIN Q3 follow-up interviews and urine tests.		O	
<b>Opioid Days of Use:</b> Days of opioids and/or heroin use summed over the GAIN-Q3 follow-up interviews.		O	M
<b>Opioid Overdose:</b> Number of opioid-related overdose[s] summed over the GAIN-Q3 follow-up interviews.		O	
<b>Opioid Related Fatality:</b> Any ICD-10 cause of death related to opioid overdose (T40.1, T40.2, T40.3, T40.4, T40.6, X42, X44, X62, X64, Y12, Y14) in CDC death records.		O	
<b>Opioid Use Disorder:</b> The average of 11 past 90-day items on the Opioid Use Disorder Scale (11 DSM-5 symptoms) self-reported from the GAIN-Q3 follow-up interviews			O
<b>Physical Health:</b> The average of 5 past 90-day items on the Health Problem Screener (worried about health, pain, health kept participant from meeting responsibilities) from GAIN-Q3 follow-up interviews.			O
<b>Mental Health:</b> The average of the past 90-day items across the Internalizing (symptoms of depression, anxiety, trauma, suicide) or Externalizing (symptoms of attention deficit, hyperactivity, conduct, gambling) Disorder			O
<b>Cost of Health Care Utilization:</b> Sum of the quarterly costs of health care from the GAIN-Q3 follow-up interviews; based on the frequency of health, mental health or substance-related ED visits, hospitalizations, residential treatment, outpatient surgery, MAT, intensive outpatient, outpatient treatment days/times multiplied by their respective costs using published estimates by health economists, adjusted for inflation using the CPI.			O
<b>Key:</b> R=Randomization, O=Outcome, M=Mediator			

### 3. Inclusion and exclusion criteria

The study will target individuals who have received naloxone administered by first responders within the past week to reverse an overdose, but who have not entered into MAT. Inclusion criteria are: a) experienced an opioid overdose reversed with naloxone administered by first responders on a participating team within the past week, b) not in treatment during the past 30 days, and c) screen positive for an OUD. For logistical reasons, we will exclude anyone who is: d) under age 18, e) unable to speak and understand English, f) not residing in Chicago, or g) cognitively unable to provide informed consent.

### 4. Sample size and power calculation

We plan to recruit and randomize 350 participants over 24 months. There should be 99% or more power to determine the direct effect of RIMO on the primary outcome of time to MAT initiation (H1a) assuming a sample size of 350 patients, randomized into two groups of 175 each, interviews at 4 time points for the main analysis (baseline, and 3, 6, and 9 months post-randomization), our average completion rate of 94+% per follow-up wave, and a moderate to large effect size of  $d=3.0$ . This expected effect size was based on the natural log of the odds ratio ( $\text{Log}^e(\text{OR})=d$ ) of initiating MAT ( $\text{OR}=20.2$ ) from RIMO Pilot study (Scott et al., under review). For the other tests of direct effects, the effective n for power calculations in repeated measures analysis varies between a lower bound of the number of unique people per group ( $N=175$  people), and an upper bound of the number of people randomized plus the completed follow-up interviews or 668 observations per group ( $O=(175 \text{ people at intake} + \text{average of } 94\% \times 175 \text{ people} \times 3 \text{ follow-ups})$ ) as a function of the intra-class correlation coefficient (ICC) associated with the individual and the number of repeated measures (RM) per person ( $\text{effective } n'=O/(1+\text{ICC}(\text{RM}-1))$ ). In our prior studies, ICC of the other dependent

variables ranged from .13 to .34. Thus the effective n= range from 429 to 398 per group and be capable of detecting an effect size of  $d=0.2$  or more with 80% power for a two-tailed test of  $p<.05$  of effect sizes  $d=.2$  or more. For mediation analysis, the tests should also have 80%+ power for a 2-tailed test of  $p<.05$  and an indirect effect size of  $d=.2$  or more.

**TRIAL MANAGEMENT**

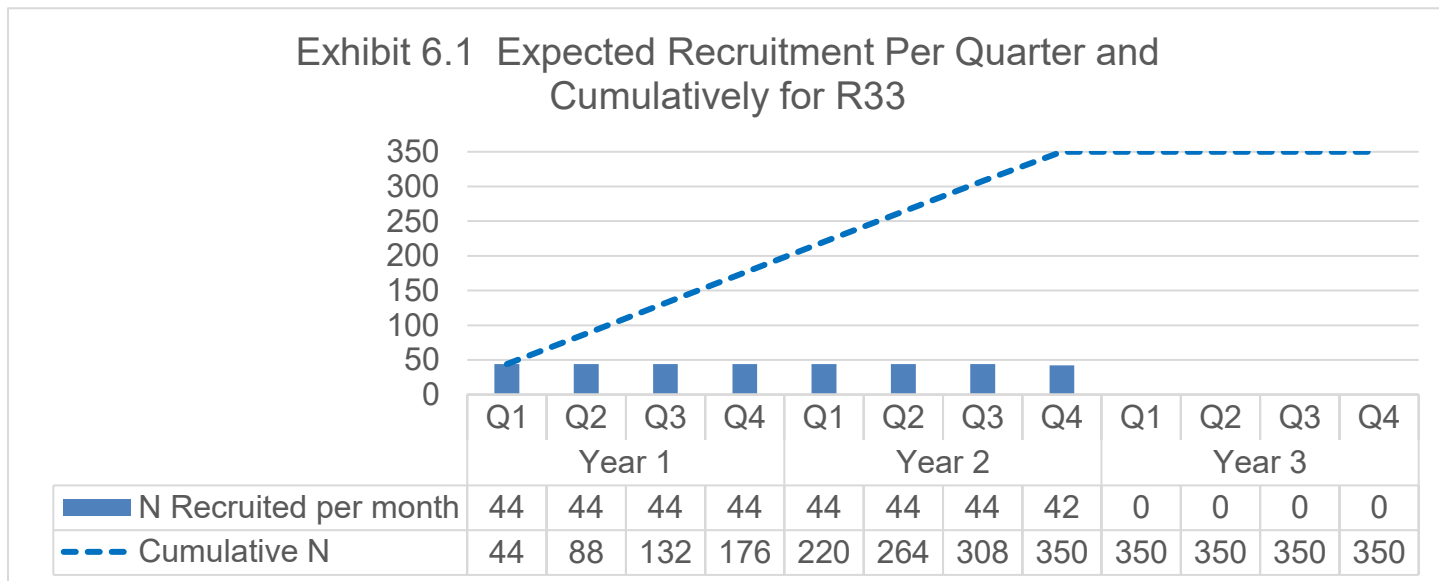
**5. List of participating enrolling clinics or data collection centers**

Participants will be recruited in the City of Chicago through partnerships with the Chicago Fire Department (CFD) and Police Department (CPD). The other data collection/intervention center sites include:

- The primary sites for training, office visits, coaching, managing the intervention, and conducting the assessments will be Chestnut’s research office at 221 W. Walton St., Chicago, IL 60610 under the supervision of Dr. Scott.
- The cloud based server for SARC, GAIN, and other data collection 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.

**6. Planned enrollment timetable**

Exhibit 6.1 shows the expected recruitment per quarter and cumulatively for the RIMO R33.



**7. Target population distribution (gender, minorities, etc.)**

Based on ambulance responses involving one or more naloxone administrations to reverse opioid overdoses within the Austin and Englewood neighborhoods, there were 946 encounters (79 per month) with people age 18 or older in 2016. Based on this data, we expect to recruit 14 to 16 people per month and that the participants will be: 25% female; 12% Hispanic; 72% Black, 15% White, 13% more than one race, and less than 1% other; and 99% were age 21 or older. Note that in the pilot study (n=33) the sample was 27% female, 15% Hispanic, 67% Black, 9% White, and 24% reporting other or multiple races.

**DATA MANAGEMENT**

**8. Data acquisition and transmission, data entry methods**

The study team will develop MOUs and Business Associate Agreements with relevant study partners for their participation in the study and HIPPA compliant exchange of information. These will formalize: (1) participation of CFD and CPD on the study advisory board and in trainings on and implementation of study procedures for first responders to solicit consent for contact from individuals following naloxone administration; (2) involvement of the IL Opioid STR project representatives in the study team and its advisory board; and (3) involvement of MAT providers in the target communities and the procedures for communicating with the study team and obtaining permission for sharing information.

All key research staff at CHS are or will be trained on the principles and process of informed consent through the Protecting Human Research Participants (PHRP) human subjects research online training program (<https://phrptraining.com>) and good clinical practice for clinical trials (<https://gcp.nidatrainig.org>) and then tested by their supervisors. All informed consents will be audiotaped for random review. If problems arise from the review, the PI and Co-PI will meet with staff to correct the problem and meet with the participant when needed to clarify any potential confusion.

The first responders will follow their standard practices for obtaining contact information from individuals following naloxone administration (i.e., name, address, phone number). For those who are alert and oriented, first responders will ask one additional question of the participants, which is whether they are willing to be contacted by someone in a few days to see how they are doing and talk about available help. If they respond affirmatively, first responders will request their signature on a form indicating their consent to share their contact information with the study investigators who will contact them, optimally within 48-72 hours. Finally, all individuals, whether or not they consent to release their information, will be provided with a brochure listing MAT providers in the local community. Research staff will pick up the release and contact forms daily from each participating firehouse and police station and document the number of people who overdosed and received naloxone and who: a) agreed, b) were not alert and/or oriented and were not asked, or c) refused. The rate of consent/refusals will be monitored against the total number of daily naloxone administrations. We will look for patterns to consent/refusal and debrief with first responders about the process. Study partners will meet every other week during the recruitment phase to monitor recruitment, discuss challenges, and develop strategies to increase recruitment, if needed. Based on the research team's success on prior studies tracking and locating participants, we expect that research staff will successfully contact approximately 75% of participants by telephone or through direct outreach. As reported in the initial focus group, we expect that almost all will currently be using opioids or heroin. Upon contact, research staff will screen individuals for eligibility based on study inclusion criteria; if eligible, they will be invited to the research office to complete the informed consent and baseline interview and will be randomized. Transportation will be provided as needed.

The Research Manager will then use gRand Urn Randomization (Version 1.10) to randomly assign 350 participants to one of the two conditions: referral to MAT control or RIMO. Urn randomization adjusts the probability of assignment to condition in ways that simultaneously minimize differences in multiple stratification variables. The base rate will be set to 50% of each condition and adjusted over time to simultaneously balance on multiple participant characteristics (gender, race, age, community) and baseline measures of key outcomes including days of opioid use in the prior 90 days, lifetime number of overdoses, high severity (3+ symptoms) on lifetime OUD, health problems, mental health symptoms, and high quarterly health care costs (more than \$7,600 dollars). The Research Manager will enter the information into the program, generate the assignment, inform participants of their group assignment, and describe the next steps. Research interviewers will be kept blind to the condition assignment for study participants.

Participants assigned to the "Referral Only" group will receive a brochure that includes a list of MAT providers in Chicago, and their location, telephone number, hours of operation, adjacent bus lines, and type of funding accepted (e.g., Medicaid). In addition, the brochure includes a range of other SUD treatment options (e.g., residential or outpatient drug-free treatment), including office-based physicians who prescribe buprenorphine or other forms of MAT. The brochure will be given to participants in both groups at the baseline assessment. Research staff will follow a script that does not include any statements regarding motivation for treatment. At present, based on our interviews with key informants and focus group with pilot study participants, there is currently no systematic method in place for referring individuals to MAT (or other SUD treatment) either from the first responders following administration of naloxone or at the EDs following their admission for opioid-related overdose. Hence, this condition represents more than the "usual care" in the community.

Participants assigned to the "RIMO" group will have a face-to-face meeting with the Linkage Manager (LM), who will engage the participants in a discussion about their willingness to go to MAT. Based on our prior trials and the pilot, we expect this meeting to take place in 1-4 working days following the OD. LM will use motivational interviewing (MI) techniques to: 1) discuss with participants the benefits of their decision to go to treatment, including activities they might enjoy as well as things they do not like about their alcohol/substance use, 2) provide personalized feedback to participants about the status of their condition based on responses to the assessment instruments, 3) help participants resolve ambivalence about their opioid use and move them toward a commitment to change by accessing treatment, 4) address existing barriers to treatment, e.g., assess Medicaid eligibility and assist with applications, problem-solve issues regarding childcare or transportation, 5) schedule a treatment appointment, 6) develop a reminder schedule for MAT appointments, and 7) problem

solve any transportation or other challenges that arise. The LM will contact participants 2-3 times/week for at least 4 weeks to ensure that participants complete detox and/or initiate and remain engaged in MAT. This includes working with the individual and the treatment provider to minimize missed doses, which can “reset” the dosing schedule. Specifically, the LM will follow-up with the treatment agency and/or participants to determine if they showed for their intake appointments and scheduled dosing for 30 days. For participants that miss a dose, the LM will contact them to discuss barriers and ways to remove them. Additionally, the LM and MAT provider will coordinate information on the participant’s barriers to treatment engagement (i.e., scheduling, transportation) and assist the participant in problem-solving solutions to support their treatment retention. During the first 30 days, the research team will provide bus cards for those in need.

For participants who refuse the referral to MAT, the LM will use motivational interviewing (MI) techniques to explore the perceived benefits and consequences of the individual’s current opioid/heroin use, as well as explore their motivation for treatment. Using empathy and reflection, the LM will explore the issues and barriers participants face when thinking about going to treatment. Using open-ended questions, the LM will explore not only reasons the individual opted out of the referral to MAT but also the potential benefits of treatment. The LM will try to develop some discrepancy between where the participant is currently and where they want to be. The LM will use the MI technique of rolling with resistance and assure the participant that the decision is up to him/her regarding treatment - empowering the participant in the decision process and encouraging “change talk”. The LM will document the various reasons that participants cite for declining the treatment referral. Learning more about the reasons for these refusals can further inform the development or refinement of strategies for improving linkages. Our experience with other similar trials indicates that many refusals are situational or temporary in nature (e.g., illness, fatigue, sick family member) and simply re-contacting the person at a later date is, in some cases, sufficient to convert a refusal. We will routinely re-contact individuals who refuse linkage to detox or MAT to ascertain if their feelings about entering treatment have changed and continue to engage with them using MI. If the individual is not interested in MAT or other types of treatment, the LM and participant will develop an alternative action plan, which may include specific behaviors and recovery activities (e.g., carry naloxone, attend self-help, get a sponsor) to reduce or stop use.

Fidelity to the RIMO procedures for engaging and linking participants to MAT and providing ongoing recovery support will be assessed in two ways. For RIMO meetings at baseline and 3, 6, and 9 months post-randomization, the LM will document the participant’s need for treatment, treatment initiation and retention. Staff will also audio record all RIMO sessions and the Linkage Supervisor will review a random sample using the Motivational Interviewing Skill Code (MISC) to measure key constructs like “change talk” that are associated with positive outcomes.

To measure change, research staff at baseline, 3, 6, and 9 months post enrollment will interview patients using the 25-minute Global Appraisal of Individual Needs Quick Version 3 (GAIN-Q3). The GAIN-Q3 includes 4-6 symptom count screeners that are correlated .9 or more with the 11 to 43-symptom version in the full GAIN. It also has cut points with excellent (~90%) sensitivity, specificity, and area under the curve (AUC) relative to the full GAIN in 9 problem areas related to substance use disorders, physical health, internalizing and externalizing mental health disorders, as well as school, work, stress, HIV risk behaviors/victimization, and crime/violence. The days of use measures have been validated against the Timeline Follow-back, collateral reports, and urine and saliva tests. The GAIN-Q3 also includes summary measures for health care utilization, functional impairment, quality of life, and life satisfaction. The GAIN-Q3 includes the behavioral health screener and health care utilization measures that have been recommended by NIH’s Phenx common data elements as two of the most reliable, valid, efficient, and inexpensive tools in the field. At each follow-up, the Q3 follow-up will be supplemented with a) a section on overdose and naloxone experiences, and b) symptom counts from the OUD scale. Data will be collected via a cloud-based computer program that controls ranges and skip outs and identifies major inconsistencies for interviewers. Drs. Scott and Dennis will train and supervise research staff. All interviews will be digitally recorded and a random sample reviewed for quality assurance. Our QA process has previously produced consistently good psychometrics across staff, sites, and mode (in person vs. by phone). The GAIN manual, norms, and a list of over 400 GAIN-related publications are available at [www.gaincc.org](http://www.gaincc.org).

Wherever possible, the interviews with the GAIN-Q3 and other supplements will be done via computer assisted interview using chestnut’s existing HIPAA and HITECH compliant cloud-based software (see [www.gaincc.org](http://www.gaincc.org)). In use by over 3,500 agencies in all 50 states, this software incorporates skips, range and error checking in real time. It helps interviewers to go through complex question matrices of questions with fewer errors, leaves less missing data, and provides an immediate validity report to reduce inconsistencies

across multiple items. In the event that the data is collected on paper and pencil, this same software can be used for data entry.

The team will implement Dr. Scott's follow-up procedures which have reliably produced over 90% follow-up rates across studies involving over 70,000 patients regardless of age (adolescents, young adults, adults) or population (homeless, justice involved, undocumented) over follow-up periods ranging from 3 months to 19 years. This includes follow-up interviews with 90% of the adolescents in the team's prior studies from up to 42 months intake. Steps include: a) contacting participants within 24-48 hours to collect additional locator information and mailing a schedule card for the next interview; b) receipting information in an MIS; 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; 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; and m) implementing a no-show protocol. Progress will be monitored with daily management reports.

## **9. Data security and protecting confidentiality**

All servers, PCs, and web 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 people 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.

Prior to using data for analyses, all data sets are de-identified by a) stripping all participant-identifying information such as name, driver's license number, and social security number from all interview notes and electronic data files, b) replacing participant research ID with a new randomly assigned ID (requiring multiple linkage files in hands of different people to re-identify an individual), and c) replacing dates with days from randomization to make deduction more difficult. As noted above, all staff accessing the data must complete human subject training and sign an agreement to respect the individual's privacy, not to attempt to re-identify them, and not to report out their individual answers in a way that someone else could re-identify them. Electronic study information will be kept in a file server that is secure, encrypted, and protected by password. Only authorized people will be allowed access to 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.

## **10. Statistical analysis plan**

Missing data. Participants will complete their baseline interview prior to randomization. Based on prior studies conducted by the applicants, it is expected that approximately 90% or more of the 3, 6, and 9-month post-randomization interviews will be completed. Among these completed interviews, prior studies conducted by the team indicate that less than 1% will have additional missing data on any of the core items required to test the study hypotheses. Multiple imputations will be used to replace the small amounts of missing data to allow 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.



Survival Analysis for Time to MAT Initiation and Time on Medication (Aim 1). The primary outcome is the days from randomization until the initiation of any kind of MAT. Relative to the referral only control group, the direct effects of RIMO on reducing the days from randomization to initiation of any MAT (H1a) and increasing the days on medication after initiation (H1b) will be evaluated with a Cox Regression model using IBM SPSS version 24 with random assignment to RIMO as the main predictor, as the investigators have done in earlier experiments. It will be examined after the point of randomization and after each follow-up interview. Survival analysis incorporates information about censorship (e.g., death, people who were not admitted to MAT within 9 months) and can incorporate covariates if needed. The output includes a case summary (e.g., missing data, other problems, descriptive statistics) and an evaluation of each term (e.g., beta, its standard error, Wald, its probability, the odds ratio, the 95% confidence interval for the odds ratio). The beta can also be converted to a Cohen's effect size *d*. All analyses will use an intent-to-treat approach (i.e., participants are analyzed as assigned regardless of their actual level of participation in RIMO). We will also conduct a secondary analysis of the time to MAT initiation after each RIMO checkup to understand the pattern over time as we have done with earlier experiments.

Direct Effects of RIMO on MAT (Aim 1). Relative to the referral only control group, the direct effects of RIMO on reducing dropout and receiving more total days of MAT will be evaluated using a multilevel structural equation modeling (MSEM) with mixed effects in MPlus (version 7.4). The analysis will model observations (Level 1) nested within participants (Level 2), with participants modeled as a random factor anchored on the baseline version of the dependent variable. Randomization to RIMO will be modeled as a Level 1 predictor. We will check for the need to use models that adjust for counts or zero saturation.

Direct Effects of RIMO on Secondary Outcomes of Time to Relapse, Opioid Use and Overdose (Aim 2) and Death, OUD, Health, Mental Health, and Health Care Utilization (Aim 3). Relative to the referral only control group, the direct effects of RIMO on time to first relapse (H2) will be evaluated with a survival analysis similar to Aim 1 H1. It will be examined after the point of randomization and after each follow-up interview. The direct effects of RIMO on days of opioid use (H2), opioid overdoses (H2), opioid-related fatality (H3), symptoms of OUD (H3), physical health problems (H3), mental health symptoms (H3), and the cost of health care utilization (H3) will also be evaluated using a series of MSEM with mixed effects in MPlus modeled in the same way as above. Most of the above variables are relatively continuous, but we will check for the need to use models that adjust for counts or zero saturation. For opioid-related fatality (H3), we will define the dependent variable as dichotomous in MPlus (equivalent to using logistic regression).

Indirect Effects of RIMO (Aims 2 and 3). To evaluate indirect effects, we will determine the extent to which the direct effects of RIMO on the above dependent variables are changed by of days of MAT received (H2 & H3) and/or days of opioid use (H3) using the Preacher and colleagues framework for testing mediation in MSEM with REML in MPlus. Loss of statistical significance in the path coefficient from the intervention conditions to the other outcome variables would indicate full mediation; a reduction in the path coefficient would indicate partial mediation. Change 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 change.

## **QA AND QC PLAN**

### **11. Procedures in place to ensure the integrity and validity of the data**

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. 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 principles and process of informed consent through the Protecting Human Research Participants (PHRP) human subjects research online training program (<https://phrptraining.com>) and good clinical practice for clinical trials (<https://gcp.nidatrainig.org>) and then tested by their supervisors. All informed consents will be audiotaped for random review. If problems arise from the review, the PI and Protocol Monitor will meet with staff to correct the problem and meet with the participant when needed to clarify any potential confusion.

All PCs and web 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 people 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.

## **12. Procedures to guarantee the accuracy and completeness of the dataset**

Drs. Dennis and Scott will train and supervise research staff. Interviews are checked for completeness and relative to urine tests at office visits. All interviews will be digitally recorded and a random sample reviewed for quality assurance. Our QA process has previously produced consistently good psychometrics across staff, sites, and mode (in person vs. by phone). The GAIN electronic interview conducts range checks, makes simple and complex skips, and allows immediate consistency checks. If an interview needs to be done with paper and pencil (e.g., jail, hospital), the interviewer will field edit it followed by a second edit to verify that key fields are complete, provide feedback and/or get clarification of questions, and mark any missing/bad data. The Research Manager will review inconsistent or missing data with the interviewers. When the data are keyed, the computer system will again check for range and consistency across multiple items. Weekly management reports will be used to monitor performance and error reports will be reviewed weekly until there are no major problems (or when there is new staff), then monthly thereafter. All GAIN data will be checked for unexpected patterns of increased or decreased activity.

## **REGULATORY**

### **13. Reporting process for AEs and SAEs**

All expected and unexpected AEs and SAEs are reviewed by the PI and reported to the study's DSM monitor, Chestnut's IRB, and NIDA within 48 hours.

### **14. SAE reporting in medication trials: FDA, IRB, and NIDA**

Not applicable.

### **15. SAE reporting in non-medication trials: IRB and NIDA**

Any unexpected SAEs and or SAE related to the research are documented by staff, reviewed by the PI and reported to the study's DSM monitor, Chestnut's IRB, and NIDA within 48 hours.

### **16. Process of reporting IRB actions to NIDA**

Chestnut's IRB reviews any unexpected SAE or DSM concerns as they come up and every all AE/SAE for the project annually. They give their recommendations in writing that is reported to the NIDA as part of the annual continuation and can contact NIDA directly if they have concerns.

### **17. Process of changes or amendments to the protocol**

Any major changes or amendments to the study protocol (e.g., change in design, hypotheses, sample size, inclusion criteria) will typically be discussed in advance with the study's DSM monitor, Chestnut's IRB, and NIDA. The exception would be emergency steps taken to protect the safety or privacy of the study participants. In that event, we will notify the study's DSM monitor, Chestnut's IRB, and NIDA. Other minor changes (e.g., updates to software, adjusting instructions in surveys, updating applications) will be reported as part of the annual updates.

## **TRIAL SAFETY**

### **18. Potential risks and benefits for participants**

Though relatively low, there are potential risks associated with this study that we acknowledge to the participants during our consent process, intake assessment, and follow-up interviews, including:

- unauthorized disclosure of sensitive information collected by research staff during interviews
- discomfort may arise from issues that are addressed in the interview (e.g., family relationships, school, self-esteem, continued use)
- required disclosures if participants report a recent situation involving child abuse or neglect, or threat of harm to themselves or others

Participants may benefit directly by receiving help to access MAT for opioid use disorders, to stay in treatment, and to sustain recovery. Participants will be interviewed at baseline prior to randomization and at 3, 6, and 9 months post-randomization; they will be compensated at a rate of \$25 per assessment (interview and urine) for a possible total of \$100.

Participation may also benefit other people in the future by helping the field learn more about optimal mechanisms for linking individuals to MAT following an opioid overdose and factors that promote their sustained treatment retention and improvements in quality of life and overall psychosocial functioning and reduce poor health outcomes and risk of death.

#### **19. Risk mitigation plan (management of SAE and other study risks)**

As noted in section 11, we require all staff to get certified on human subject training and use HIPAA/HITECH compliant secure web services to house all of the data and limit access to be also encrypted means and role/password based by person. Expected negative events have are being documented both through the surveys/records (for expected events) and negative event forms (for unexpected events) - discussed further below. All consent/locator forms are kept in separate record systems/ locked files than the survey data. No confidential fields (e.g., names) are downloaded and data are further de-identified by replacing the dates with days from randomization, double-checking all text fields for any potential identifiers, and field research id with a second analytic research ID. The latter means that two linkage files are required to re-identify a person – one held by the analytic team in Bloomington-Normal and a second held separately by the field team in Chicago. No person will be identified in any study report. As discussed further below, expected and unexpected problems that have occurred are also reported to the DSMB, IRB, and NIDA for further review.

#### **20. Trial stopping rules**

The primary stopping rule would be based on a statistically significant ( $p < .05$ ) and clinically significant ( $d < -0.2$ ) finding in the wrong direction (i.e., experimental group doing worse than the control group) on the primary outcome, substance frequency scale. In consultation with the DSM monitor, the trial could also be stopped (or modified) if other unexpected issues come up suggesting that the intervention or research procedures are causing harm.

#### **21. Process of AE/SAE collection, assessing by PI and/or medical monitor and reporting**

Our study definitions of critical events to be monitored are:

- The expected Adverse Events (AE) measured directly as part of baseline and quarterly observations are the days of problems from AOD 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 incarceration. Deaths are documented both in follow-up logs and (if we have firsthand or reliable information) as in the negative event report discussed below.
- Unexpected AE/SAE (including deaths where we have details) will be documented the same day we find out about it 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).

#### **22. AE/SAE follow-up plan**

The PI will work with the study's DSM monitor, Chestnut's IRB and NIDA to anticipate and minimize the risk of SAE and other study risk in advance. The PI will also monitor study implementation to verify assumptions and performance relative to these risks in general, including training staff to report unexpected SAE/AE and other study risks so that they can be reviewed and reported. Where there are more than expected SAE/AE, unexpected SAE or other study risks, the PI will work with the DSM monitor and Chestnut's IRB to modify procedures to address them and, if necessary, decide to suspend or stop the study.

### **TRIAL EFFICACY**

#### **23. Plan for interim analysis (if applicable)**

Each annual DSM report will include an analysis of efficacy data. If any annual review reveals a significant difference in dependent variables (or AE or SAE) that goes AGAINST the experimental condition or

appears to be related to a study specific procedure, we will consult with the DSMB on the need to modify the protocol, study procedure, or even stop the study. As noted above, the stopping rule would be based on a statistically significant ( $p < .05$ ) and clinically significant ( $d < -0.2$ ) finding in the wrong direction.

## **ADMINISTRATION OF DSM PLAN**

### **24. Responsibility of data and safety monitoring**

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 an AE, SAE, or other, the degree to which it is related to intervention or research procedures, and document any actions taken (with participant, reporting to IRB, reporting to DSMB). Any events that are attributed to the intervention or research procedure and any sentinel event will be reported within 48 hours to the DSMB, IRB, and NIDA for further review. We will use The Joint Commission (TJC) 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.” A copy of the annual report, the findings and any correspondence will be forwarded to Chestnut’s IRB and our NIDA project officer as part of annual reporting.

### **25. Frequency of monitoring**

All interviews and intervention sessions will all be recorded. All will be reviewed until each staff person is certified. After that 2 recordings per person per month will be reviewed to sustain fidelity (more will be reviewed if problems are identify). Data will be downloaded cleaned and checked quarterly for quality assurance. The DSM Plan will be updated and reviewed by the IRB and DSM during the quarter prior to going into the field. The annual report will be given to the DSMB for external review approximately 2 to 4 weeks before our continuation is due to NIDA. Any directly observed or caused serious adverse event will be documented on the negative event form, reviewed and the PI and submitted to the DSMB, IRB, and NIDA within 48 hours.

### **26. Conflict of interest**

The investigators have no conflicts of interest to declare.

### **27. Content of DSM report**

Annual reports of data collected to date will include an enrollment update, the status of retention and disposition of participants (active, completed, and terminated), reviews of case flow, checks on randomization, implementation, method checks on measures, preliminary outcome analyses, expected and unexpected AE/SAE, all negative event forms, and any regulatory issues (amendments, protocol deviations, IRB reports, and QA issues).

## **DSM BOARD**

### **28. Members and affiliations**

Our independent data safety monitor is:  
Savita Prakash, Ph.D.  
AMAR International, Inc.  
11710 Plaza America Dr., Ste.200  
Reston, VA 20190  
Phone: 703-871-5204  
Email: [spakash@amar-international.com](mailto:spakash@amar-international.com)

### **29. DSM conflict of interest**

Dr. Prakash has no conflicts of interest to declare.

### **30. Frequency of meetings**

The annual report will be given to the DSM for external review approximately 6 weeks before our continuation is due to NIDA. They will then send feedback in writing and meet with the team as needed to go over any issues. The DSM will also consult with the PI as needed over plans to make any changes after any SAE.

**31. Monitoring activities**

The study is designed to comply with the Data Safety Monitoring Board Standard Operating Procedures (SOP) originally developed for NIDA's Criminal Justice Drug Abuse Treatment Outcome Study (CJ-DATS), which Dr. Michael Dennis chaired, and to be consistent with the Consolidated Standards of Reporting Trials (CONSORT; [www.consort-statement.org](http://www.consort-statement.org)), which has been published by the editors of over 60 major journals.

**32. Reporting DSM minutes to IRB, NIDA, and FDA (if applicable)**

Minutes from DSM meetings will be provided to Chestnut's IRB and NIDA upon request.