A Phase II Randomized Trial to Assess the Effectiveness and Safety of the ID-Cap System for Medication Ingestion Monitoring and Enhancing Adherence

In pharmacotherapy trials involving drug-dependent individuals, medication compliance is a significant issue, as rates tend to be low and adherence to medication may predict improved outcomes (Baros et al, 2007; McRae et al, 2004; O'Brien et al, 1996; Somoza et al., 2010). However, methods commonly used to determine compliance may result in inaccurate measurement of adherence. For example, in a pharmacotherapy trial for cocaine dependence, a comparison of an electronic medication event measurement system (MEMS), self-report, and a biochemical tracer (riboflavin) found that MEMS-based estimates of compliance were substantially lower (28%) than self-report (87%) or riboflavin (78%) (Mooney et al, 2004). Although MEMS are widely regarded as the gold standard measure of patient compliance, a critical shortcoming of this approach is that actual medication ingestion is not measured; rather, the system is limited to registering times when the closure is opened and when it is closed. Further, the MEMS is not able to transmit real-time compliance data to a clinical site and as such there is limited opportunity to intervene if non-compliance is suspected. It is therefore essential to develop measurement systems that not only accurately and objectively measure compliance, but can also have the potential to increase compliance in difficult to treat disorders such as addiction. To achieve this aim, we propose to assess the effectiveness and safety of the ID-Cap-M, a novel compliance measurement device, in a healthy population. Forty healthy individuals will be recruited and randomized into one of two intervention groups: (1) a group receiving a standard capsule containing 50mg of riboflavin to be ingested once daily and dispensed with a MEMS 6 TrackCap (n=20), and (2) a group receiving an ID-Cap-M containing 50mg of riboflavin to be ingested once daily in which participants are contacted and compliance encouraged if the ID-Cap is not ingested as directed (n=20). Specific aims and corresponding hypotheses of this clinical investigation include:

Aim 1: To assess the effectiveness of the ID-Cap-M system for medication ingestion monitoring and enhancing medication adherence.

Hypothesis 1a: The ID-Cap-M system will detect over 95% of medication ingestion events as ascertained by doses of medication recorded by the ID-Cap System that are taken as prescribed (once daily and on time with use of ID-Cap System as instructed) over those scheduled.

Hypothesis 1b: The ID-Cap-M system will have an advantage over the MEMS caps on monitoring and enhancing medication adherence expressed by a proportion of daily medication doses reported by the system to be ingested (ID-Cap System) or accessed (MEMS Caps) as prescribed (defined as within the scheduled administration time) over the study period.

Exploratory Aim 2: To assess the safety of the ID-Cap-M system when used in a healthy population by documenting the frequency and severity of adverse events.

Exploratory Hypothesis 2: Participants randomized to receive the ID-Cap-M system will report similar rates of adverse events as participants randomized to receive standard capsules.

Overview: The primary objective of the clinical trial is to evaluate the acceptability, tolerability, and efficacy of the ID-Cap-M in a healthy population. The primary outcome will be medication compliance as measured by the proportion of days adherent to taking medication over a four week period.

Subjects: 40 participants between the ages of 18 and 65 will be recruited over a 10-month period. Additional inclusion criteria include ability to provide informed consent, functioning at an intellectual

level sufficient to allow accurate completion of assessments, and having a Body Mass Index (BMI) below 35. Exclusion criteria include women who are pregnant, nursing or of childbearing potential and not practicing an effective means of birth control; subjects with evidence of a significant medical condition which may affect capsule passage (including but not limited to acute gastroenteritis, Crohn's disease, small bowel tumors, intestinal adhesions, ulcerations, and radiation enteritis); subjects with a history of hypersensitivity to riboflavin or any other capsule component; subjects with embedded electronic devices; subjects with a current major psychiatric disorder as these may interfere with assessment measures; subjects meeting DSM-V criteria for moderate to severe substance dependence (other than nicotine or caffeine) within the past 60 days; and subjects who, in the investigator's opinion, would be unable to comply with study procedures or assessments, or would be unacceptable study candidates (e.g., poses threat to staff).

Recruitment: Subjects will be primarily recruited through media and internet advertisements. "Respondent-Driven Sampling" (RDS), will also be used to enhance recruitment of the sample (Heckathorn, 1997). The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs". Each eligible participant who completes an interview will be given coupons to pass on to other potential participants. The coupons will have a unique code linked to the person who passes them out. A referral will be instructed to call the site offices for screening and, if eligible, an appointment for further evaluation. If a referral completes the screening process and is eligible for the study, the participant who referred the person can redeem the coupon for $20. We have an active recruitment network, and have consistently surpassed recruitment goals with studies in this population.

Screening/Assessment: A quick screen will be used to initially determine study eligibility. This questionnaire is focused on inclusion/exclusion of psychiatric diagnoses, medical status, and ability and willingness to complete study procedures. Potential subjects will be given a full description of the study procedures and asked to read and sign an IRB-approved Informed Consent Form if interested in participating. Appropriate modules of the Mini-International Neuropsychiatric Interview (M.I.N.I.) will be used to assess exclusionary psychiatric diagnoses (Sheehan et al, 1998). A general medical history and physical exam will also be performed to ensure that the subject is eligible to participate. Urine drug screens will be performed at the screening visit in order to rule out substance abuse. For female participants, a urine pregnancy test will be completed prior to urine drug screening.

Group Assignment/Intervention: After inclusion into the study, participants will be randomized into one of two intervention groups. Group 1 (n=20) will receive a standard capsule containing 50mg of riboflavinto be ingested once daily and dispensed with a MEMS 6 TrackCap. Group 2 (n=20) will receive an ID-CAP-M containing 50mg of riboflavin to be ingested once daily. Their compliance will be measured by data collected by an e-Tect reader worn around the neck on a lanyard. Participants randomized to this group will also receive reminder calls and/or text messages to ingest the study medication if a signal is not sent from the e-Tect reader to the study team within one hour of the end of the scheduled medication administration time window. In the event that a daily pill detection is not obtained for a subject in Group 2, but they report taking the pill as directed, they will be asked to come in to the clinic to provide a urine sample for riboflavin assessment. Group 2 participants will be provided with a loaner smartphone for e-Tect application download if they do not own a personal one or do not wish to use their own. The smartphones will be activated by a data plan, and will be of no cost to the participants. All applications of the phone will be disabled with the exception of the e-Tect

software needed to transfer data. Providing the necessary technology will prevent the exclusion of individuals without smartphone access or those who cannot afford to pay for a smartphone data plan. Group 2 will also provide biometric data for compliance measurement, specifically ECG. These measurements will be collected by their eTect reader.

Study visits: The study duration will be approximately six weeks. At the initial randomization visit, participants will be trained on use of the devices (MEMS 6 TrackCap for Group 1 and biometric data collection/ID-Cap-M for Group 2) and medication administration will be observed. A 30-day supply of study capsules will be dispensed. Participants will be instructed to take each dose by 12PM daily. Participants will return to the clinic approximately five weeks (within one week following last dose) after their initial randomization for an End of Study (EOS) visit to discuss overall medication compliance and return their study equipment (pill bottles, unused capsules if any, and MEMS 6 TrackCap or ID Cap Reader). For those in Group 2, passage of ID-Caps will be confirmed at this visit via abdominal x-ray.

Safety Assessment: Adverse events (AEs) will be assessed at the End of Study visit. The research clinician will identify potential adverse events by asking the subject a question such as: "Have you had any problems or side effects since we saw you last (such as flu, headache, nausea, or other problems)?" The type of AE, severity of AE, and relationship to the study intervention will be recorded. At their initial randomization visit, subjects will be given detailed information regarding clinic contact procedures during and afterhours should this be necessary during their study participation. An abdominal X-ray will also be completed at study completion to verify passage of the capsules from the gastrointestinal tract for those in Group 2.

Follow-up Plan: In the event that an adverse event occurs during the study, a subject will be followed to resolution. Participants will be provided incentive compensation to attend the EOS visit and return the MEMS 6 TrackCap or e-Tect reader and cell phone (if one was provided).

Compensation: Subjects will be compensated $30 for screening, ($20 for interview, $10 for H&P). They will be compensated $250 for the End of Study visit ($100 for attendance and $150 for return of their MEMS 6 TrackCap or ID Cap Reader). If a Group 2 subject did not return for an unscheduled urine sample as requested during the study, they will receive $50 for attending the EOS visit (versus $100).

Data Management and Reduction: All paper-based assessments (other than laboratory reports) will be entered into REDCap, a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides an intuitive interface for data entry (with data validation), audit trails for tracking data manipulation, and automated export procedures for data downloading to statistical packages such as SPSS and SAS. Completed assessments will be entered within two weeks after the information has been collected from the subject. Quarterly database management and data integrity audits will be conducted and reports submitted.

Statistical Methods: Univariate descriptive statistics and frequency distributions will be calculated for all variables. Departures from distributional assumptions for the proposed parametric methods will be identified and appropriate transformations of the data will be applied or alternative procedures (semi/non parametric methods) will be employed. Values for demographic, clinical, and other prognostic variables will be compared for imbalance across treatment groups. ***Aim 1:*** The hypothesis

that the ID-Cap-M will improve compliance will be tested by comparing the number of medication adherent days (defined as ingestion of dose of medication within one hour of scheduled time) in the group receiving the ID-Cap-M with the group using a MEMS 6 TrackCap. The primary analysis of the difference in the number of adherent days will be done using a two group ANOVA model. Additional model analysis will be conducted assuming a binary pattern of responses on each day and fit into a Generalized Linear Model using a Generalized Estimating Equations (GEE) framework. ***Exploratory Aim 2:*** To test the safety and tolerability of ingestion of the ID-Cap-M versus standard capsules, the number of adverse event reported in the 20 subjects taking the ID-Cap will be compared to the number of events in the 20 subjects assigned to standard capsules. Analysis will be performed using a Pearson Chi-Square test statistic.

Other Statistical Considerations: The primary method of analysis will be through the use of the intent to treat sample where missing compliance data will be deemed non-adherent. However, other methods of missing data analysis will be employed and a sensitivity analysis of the various methods will be presented.

Sample Size Justification: The proposed study intends to evaluate the feasibility of inclusion of ID-Caps to monitor compliance in medication trials involving substance abusing subjects. The current study is a 30-day efficacy evaluation of the ID-Cap-M versus MEMS 6 TrackCap***. Aim 1***: With 20 subjects receiving the active ID-Caps and 20 receiving MEMS 6 TrackCap, we will have 80% power with a two sided α=0.05 to detect an effect size of 0.95 (Cohen's *d*), which is equivalent to a difference of 0.95 adherent days between the two study groups for each unit in the standard deviation (example: with a SD of 10 days, we will be able to detect a difference of 9.5 days between groups)..

Design Considerations: *Choice of study population.* The determination was made to conduct this initial tolerability and feasibility trial in healthy individuals. After establishment of safety and efficacy in this population, subsequent studies will be conducted in drug-dependent populations. *Use of riboflavin.* Riboflavin is a water-soluble vitamin; it has no psychoactive properties and is excreted in the urine. A dose of up to 150 mg riboflavin daily has been shown to be well-tolerated by patients and easily measurable in patients' urine at levels 10-fold greater than normal using chromatographic separation and flurometric detection (Anton, 1996). As riboflavin is commonly used as a compliance measure in medication studies (Dubbert et al, 1985; Del Boca et al, 2006), it was considered an appropriate comparison marker to include.

Timeline: As we have an active recruitment network and trained staff in place, we anticipate minimal time required for study start-up. Given our previous recruitment rates for non-treatment studies (7 participants/month) we anticipate completion of the clinical trial within 12 months.

HUMAN SUBJECTS RESEARCH

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

Admission into the study is open to men, women, and children 18 to 65 years of age, and to all racial and ethnic groups. We anticipate we will screen (by telephone or in person) about 60 potential subjects. A total of 40 healthy men and women will be enrolled. We will recruit subjects from multiple

sources, primarily through advertising in local media via television, newspaper, and word of mouth among subjects.

Inclusion Criteria

- Must be between the ages of 18 and 65 years.
- If female and of childbearing potential, must agree to use acceptable methods of birth control for the duration of the trial.
- Must consent to random assignment, and be willing to commit to capsule ingestion.
- Must be able to read and provide informed consent.
- Must function at an intellectual level sufficient to allow accurate completion of assessments.
- Must have a Body Mass Index (BMI) below 35.

Exclusion Criteria

- Women who are pregnant, nursing, or plan to become pregnant during the course of the study.
- Must not have evidence of a significant medical condition which may affect capsule passage through the gastrointestinal tract (including, but not limited to, Crohn's disease, small bowel tumors, intestinal adhesions, ulcerations, and radiation enteritis) Must not have a current major psychiatric disorder as these may interfere with assessment measures.
- Must not meet DSM-V criteria for moderate to severe substance dependence (other than nicotine or caffeine) within the past 60 days
- Hypersensitivity to riboflavin or any other capsule component.
- Individuals with embedded electronic devices.
- Patients who, in the investigator's opinion, would be unable to comply with study procedures or assessments, or would be unacceptable study candidates (e.g., poses threat to staff).

b. Sources of Materials

1) Research material obtained from individual subjects includes questionnaires and interviews with study personnel as well as urine samples. To ensure confidentiality, all subject data will be number coded, and only the investigators will have access to the master lists of codes.
2) The research material will be obtained specifically for research purposes. Written research material obtained will be stored in the Addiction Sciences Division, in an office that is locked when not in use. Any quantitative riboflavin urine samples collected during the study will be stored in the MUSC Clinical Neurobiology Laboratory..

c. Potential Risks

Potential risks associated with capsule ingestion include discomfort in the form of pressure sensations in the esophagus upon ingestion (typically lasting less than 30 seconds), risk of endoscopy pill retention, and a rare risk of capsule aspiration upon attempting to swallow the capsule. There is the risk of breach of confidentiality.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Patients will primarily be recruited through the use of advertisements (internet, newspaper). Respondent-driven sampling will also be utilized. Medical records will NOT be reviewed to identify potential study subjects. The study PI, a Co-I, or other qualified study staff will obtain informed consent. The informed consent form includes a detailed description of the study procedures, along

with statements regarding participants' rights to withdraw from the procedure at any time without consequences. The informed consent form will be explained to subjects in easy-to-understand language, and subjects will be instructed to read the form carefully prior to signing it. Consent will be documented by the signature of the participant on the informed consent agreement, accompanied by the signature of the individual obtaining the consent.

b. Protection Against Risk

Dr. McRae-Clark and the study physician assistant will monitor for medical and psychiatric stability. All study visits will be conducted under the supervision of experienced personnel. If crisis intervention is necessary, senior staff will be available to evaluate the subject and provide an intervention or referral. If hospitalization is indicated, the patient will be hospitalized through the CDAP program at MUSC or an appropriate referral will be made. All subjects will be fully informed that they may withdraw from the study at any time without penalty. All subject records will be kept in a locked filing cabinet, and confidentiality of all materials will be maintained. Offices also will be locked at times when not in use.

Subjects will be taught about potential side effects of ID-Cap ingestion and will be closely followed by psychiatrists, a PharmD, and other members of the research team. Subjects will be excluded from participation if a medical condition is present that may impact capsule passage, and subjects will also be excluded if they have a known hypersensitivity to any capsule component. Adverse events will be assessed at at the End of Study visit, and all subjects will be provided with an after-hours emergency contact number in the event that an adverse event occurs when the clinic is closed.

To ensure confidentiality, subject data will be number coded, and only the investigators will have access to the master lists of codes. All patient records will be kept in an office that will be locked at times when not in use. The research staff understands the importance of maintaining confidentiality. This method of maintaining confidentiality has been used for several years by our research group and has been effective.

Data from the loaner smartphones will be immediately transmitted to RedCap, a secure data management system maintained at MUSC (See Section 5.3, Data Management and Analysis). These data will only be accessible by the Research Personnel and PI. Participants will be informed of these potential risks during the informed consent process and will have the option to leave the study at any point.

The smartphone application is equipped to transmit data directly into RedCap with de-identified subject IDs. Server maintenance will be conducted by Information Technology Specialists at MUSC. Once data have been transmitted to RedCap from the loaner smartphone or participant's personal smartphone, no personal information will be stored on the device. Any information that is stored on the phones will be de-identified. If the loaner iPhone is lost or stolen, devices will be reset immediately.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Possible risks to study participants include adverse reactions to ID-Cap ingestion. Benefits include a detailed physical and psychiatric assessment and referral to treatment options if needed. The minimal risks are reasonable in relation to the potential benefits to be gained from the investigation.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study may provide important information that can improve clinical trial designs for future patients.

5. DATA SAFETY MONITORING PLAN

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html). A detailed DSMP will be developed and approved by NIH program staff prior to study initiation.

5.1 Summary of the Protocol.

This application proposes to evaluate the acceptability, tolerability, and efficacy of the ID-Cap in a healthy population. The primary outcome will be medication compliance as measured by proportion of days compliant over a 30-day study treatment period.

5.2 Trial Management.

The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. The target population is described above in the inclusion/exclusion criteria.

5.3 Data Management and Analysis.

Data will be entered by research assistants directly into a computer using standard database software using REDCap. The data analysis plan is outlined in the Data Analysis Plan section.

5.4 Quality Assurance.

Quarterly data audits will be conducted. Confidentiality protections are outlined above.

5.5 Regulatory Issues.

We will apply for IRB approval prior to the initiation of the study. Potential conflicts of interest will be reported using the upcoming NIH rules for disclosure. Adverse Events (AEs)/Serious Adverse Events (SAEs) occurring during the course of the project will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. A research assistant will identify any potential adverse events during the course of the study from participant self-report and administration of the visit assessments and procedures. The research assistant will provide information to a study physician, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness. Any significant actions taken by the local IRB and protocol changes will be relayed to NIDA.

5.6 Definition of AE and SAE.

An Adverse Event (AE) is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment (ICH GCP). Any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the trial is an adverse event. A Serious Adverse Event (SAE) is defined as an adverse event that has one of the following outcomes:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,

- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect OR
- Requires intervention to prevent one of the above outcomes.

5.7 Documentation and Reporting. AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study as stated in the protocol. When a reportable SAE is identified, the research staff will notify the MUSC Institutional Review Board (IRB) within 24 hours and complete the AE report form in conjunction with the PI. The MUSC IRB meets monthly and is located at 165 Cannon Street, Rm. 501, Charleston, SC 29425. Communication with the IRB is through email, memos, official IRB forms, and online reporting. A report will also be sent to the NIH program officer assigned to the project.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the NIH program officer as appropriate within 2 weeks of the initial SAE report. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the NIDA Medical Safety Officer within two weeks of the initial SAE report.

We will report adverse events to the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) online as soon as possible, but no later than 10 working days after the investigator first learns of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

5.8 Trial Safety.
The potential risks and benefits and methods to minimize these risks are outlined above. The research staff will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if

treatment is needed. Study procedures will follow the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to Drs. McRae-Clark.

5.9 Trial Efficacy.
As this is a preliminary investigation, an interim analysis is not planned at the time.

5.10 DSM Plan Administration.
Dr. McRae-Clark will be responsible for monitoring the study. A DSM report will be filed with the IRB and NIDA on a twice yearly basis, unless greater than expected problems occur or more frequent reporting is requested. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report outcomes at the end of the trial.

5.11 DSM Board.
As this is a single-site study with a healthy population, a full Data and Safety Monitoring Board is not warranted. The subcontract principal investigator, Dr. Aimee McRae-Clark, will have overall responsibility for safety and data monitoring on a day-to-day basis. A detailed Data and Safety Monitoring Plan will be submitted to NIDA prior to study initiation.

5.12 Risk Benefit Ratio.
The assessments and questionnaires are non-invasive and have inherently minimal risks. Potential risks of concern are loss of confidentiality, and adverse events to ID-Cap ingestion. As discussed above, our research team will attempt to minimize these risks. Knowledge gained by the proposed study may be helpful in developing effective treatments for substance use disorders.

6. CLINICALTRIALS.GOV REQUIREMENTS

In accordance with Public Law 110-85, this project will be registered at the ClinicalTrials.gov Protocol Registration System Information Website prior to study initiation.

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