Study: # 6850 entitled A sequenced behavioral and medication intervention for cocaine dependence

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export data files that are easily read by statistical software packages.

C7. Data Analysis: Dr. Pavlicova, a Biostatistics Faculty member assigned to our division, has extensive experience in the analysis of clinical trial data and will design and oversee all analyses. The primary analyses in this study will be on the intent-to-treat (ITT) sample, (i.e. on all 100 randomized patients). Prior to conducting hypotheses testing we will examine all variables for the presence of outliers and deviations from normality, and transformations will be employed, if necessary. The distribution of demographic variables (ethnicity, sex, age) will be examined and described in terms of means, standard deviations, proportions and 95% confidence intervals. **[**Demographic and baseline clinical variables will also be examined as predictors of the primary outcome measure, and those found to be significant will be considered as covariates.**]**

C8. Power Analysis: [Enrolling 155 patients will afford adequate power (80%) to detect medium effect sizes (d=0.57; Odds Ratio=2.8) in the logistic regression analyses investigating response to the behavioral intervention at week 4.**]** Also, prior studies with amphetamine (Grabowski et al., 2001) and TES (Bickel, Marsch et al., 2008) suggest medium effect sizes can be reasonably expected. Continuous abstinence during treatment is a desired clinical outcome as it predicts continued abstinence during post treatment follow-up (Higgins et al, 2000). We found 33.3% of the MAS-ER/topiramate group and 16.7% of the placebo group achieved 3 weeks of continuous abstinence in our controlled pilot study. The response was 37% in the MAS-ER/topiramate group compared to 7.4% in the placebo group among the high users. We expect our placebo response to be low since individuals randomized to a medication arm will have already demonstrated little response to the CRA+CM therapy alone, the only active component in the CRA+CM/PLACEBO condition. Thus, we conservatively estimated the power (80%; significance α=0.05) with an expected response rate of 37% in the ehancement medication arm (MAS-ER) compared to 10% among those receiving PLACEBO. The primary outcome for the phase 2 analyses is the percentage of subjects who achieve continuous 3-weeks abstinence during the study. With 34 subjects in each treatment there is 80% power to detect a difference in proportions (37% vs.10%). With 50 subjects in each arm there is 90% power to detect the same difference.

C9. Intent to Treat/ Dropouts and missing data: The primary analyses will be on the Intent-to-treat (ITT) sample, (i.e., all randomized subjects according to the treatment they were assigned). We will account for dropouts by examining the primary outcome variables using (longitudinal) mixed effects models (MEM) (Brown and Prescott 1999; Diggle et al 2002) using PROC GLIMMIX in SAS®. MEMs do not require a complete set of time points to estimate the outcome variable. However, inferences from analyses with missing data are valid provided that the data are "missing at random"(Little and Rubin 1987). While 'missing at random' (i.e, the missing mechanism does not depend on the value of the unobserved outcome) is un-testable in most medical research, parametric or semi-parametric models (that both depend on the unobserved outcome value) can be used to model the missingness (Diggle and Kenward 1994; Kenward 1998; Liu et al 1999; Rotnitzky et al 1998; Scharfstein et al 1999). Comparisons of the inferences from the various models of missingness provide a measure of the validity of the 'missing at random' assumption. One can also compute a local sensitivity index which measures the change in the estimated treatment effect in a neighborhood of the 'missing at random' model (Rotnitzky et al 2001). We plan to perform a *sensitivity analysis* based on these two approaches to assess the effect of the assumption of missing 'at random' on the inference.

C10. Primary Outcome Measures: The primary outcome measure will be a binary indicator (yes or no) of at least 3 weeks of urine toxicology confirmed self-reported abstinence during Phase-2 (weeks 5-14). While the standard method for measuring cocaine use outcomes is urine toxicology, self-reported cocaine use confirmed by urine toxicology provides additional data that cannot be determined by laboratory testing alone. The reliability of self-reported cocaine use in the context of confirmatory urine toxicology testing is high; for example among 121 cocaine-dependent outpatients self-report matched the toxicology results 94% of the time (Carroll, et al., 2004). Self-reported cocaine use data will be collected using the timeline followback method for the 28 days preceding study entry and each day of the study period. Semi-quantitative urine benzoylecgonine (BE) levels will be obtained with Abbot/ADX technology. To prevent overestimation of cocaine use, we will confirm self-reported cocaine use with a modified version of a procedure developed by (Winhusen et al. 2007), a procedure we have employed in previous studies (e.g. Mariani et al., in press). Self-report of cocaine use will be accepted as a "use day" and urine samples with BE levels equal to or greater than the standard NIDA 300 ng/ml will be considered positive. A urine sample will be considered negative if it is preceded within two days by a sample with 2x or more its BE level. If none of the three days preceding a positive urine sample has been self-reported as a use day, the day immediately preceding the sample will be labeled a use day.

Primary hypothesis: *A greater proportion of patients treated with CRA+CM/MAS-ER will achieve continued abstinence compared to patients treated with CRA+CM/PLACEBO.* The effect of treatment on the

outcome (at least 3 consecutive weeks of urine toxicology confirmed self-reported abstinence) will be examined using logistic regression adjusted for covariates (e.g., baseline days/week of cocaine use): **logit(Y_{ikt}) = ß$_0$ + ß $_1$ I_{ij}^M +ß$_2$$Z_{ijk}$ + e_{ijk};** where Y_{it} is a binary outcome indicating 3 weeks of abstinence (Y_{itk} = 1, when a given individual in a treatment condition is abstinent), I_{ij}^M is an indicator for the medication treatment (I_{ij}^M = *1* for MAS-ER and I_{ij}^M =*0* for PLACEBO),), Z_{ijk} is a vector of covariates, such as baseline cocaine use, and demographic characterisitics (age, gender, ethnicity), and e_{ijk} is random error. **[**Covariate by treatment interactions will be tested for significance and the main effect, the primary hypothesis will be answered by testing the null hypothesis B_1=0. **]**

[C11. **Predicting Responder and Non-Responder status.** Analyses will be conducted to identify variables that may help predict who is more or less likely to respond to the psychosocial intervention alone. Identifying key cognitive-verbal mechanisms (see below) that predict treatment response can help provide important avenues for guiding future therapy development. This important aim will be examined using a logistic regression model within a general linear model framework where responder status at the end of week 4 is a binary outome and the predictors will be a vector of baseline covariates. Predictor variables will be entered in blocks and tested for significance (baseline commitment language, executive functioning, implicit cognition, coping skills, baseline cocaine use, and demographic characteristics (age, gender, ethnicity). Furthermore, a vector of variables representing the magnitude of change in the cognitive, behavioral, and verbal mechanisms will be tested. This later block of variables will evaluate if the response to the behavioral intervention alone is predicted by the magnitude of change in the key cognitive, verbal, and behavioral indices.**]**

[C12. Secondary hypotheses and outcomes: *Patients receiving CRA+CM/MAS-ER will demonstrate a greater reduction in cocaine use, cravings, and withdrawal symptoms, increased retention and quality of life compared to patients treated with CRA+CM/PLACEBO.* Analyses will test the hypotheses that the CRA+CM/MAS-ER group will demonstrate 1) a lower proportion of weekly urine toxicology samples testing positive for benzoylecgonine (longitudinal continuous variable); 2) lower cocaine withdrawal symptoms as measured by the Cocaine Selective Severity Assessment (CSSA; a longitudinal continuous variable), 3) lower cocaine craving as measured by the Cocaine Craving Questionnaire (longitudinal continuous variable) 4] better quality of life (Endicott et al., 1993) , and 5) greater study retention then the PLACEBO/CRA+CM group. The longitudinal continuous outcomes will be treated with longitudinal mixed effect models (MEM), where patients will be treated as a random factor. Appropriate transformations of distributions will be applied to the outcome variable if needed (for count variables, the Poisson distribution will be used). The group differences in retention is operationalized as time to dropout, which will be analyzed within a Cox proportion hazard framework. **Exploratory Analyses:** We will also test for differences in treatment outcome between the CRA+CM only condition (no medication or placebo) and each of the medication treatment arms (CRA+CM/MAS-ER and CRA+CM/PLACEBO) on the primary and secondary outcomes outlined above. Recall, this group will consist of the individuals who responded to the behavioral treatment during the 4-week run-in and were not randomized to receive either MAS-ER or PLACEBO. These exploratory comparisons will provide useful information on the relative differences between individuals needing an integrative treatment strategy against those benefiting from the behavioral treatment alone in terms of their trajectory and level of change during a treatment episode.**]**

[C13. Exploratory hypotheses: Investigating Mechanisms of Change: We propose a set of exploratory analyses to evaluate the predictive and/or moderating relationship of several key cognitive, verbal, and behavioral mechanisms on treatment response. These variables will be assessed at Baseline, Week 5 (beginning of the medication phase), and Week 14 (end of study). They include: **COGNITIVE MECHANISMS. *A. Executive Functioning*.** Self-regulation has been linked to higher order cognitive processes under the rubric of executive functioning, which predicts treatment response (Aharonovich et al., 2006). Within this domain several constructs have been implicated in substance use and treatment response **1. Working memory (Letter-Number Sequencing,** Wechsler, 1997**)**, improved working memory is associated with enhanced striatal dopamine release (Backman et al., 2011) and has been implicated as being an important process in treatment outcome (Bickel et al., 2010); The letter number sequencing task will be utlized to assess a participant's working memory. **2. The discounting of delayed rewards (Delayed Discount Program, Robles et al., 2008):** Working towards greater delayed rewards in contrast to smaller more immediate rewards is a hallmark characteristic of planned, controlled behavior. However, drug dependent individuals discount future rewards faster than non-dependent individuals and the rate of discounting predicts treatment response (Washio et al., 2011). Area Under the curve (AUC) values will be used to quantify the rate of discounting for each individual. **3. Wisconsin Card Sort,** a measure of executive functioning and cognitive

flexibility, has been related to changes in commitment language during treatment (Aharonovich et al. 2008) and is currently being used in other funded studies *(NIDA K23; An experimental model of human language and cognition in drug dependence PI: Kenneth Carpenter*). **4. The Behavior Rating Inventory of Executive Function** (Adult Version (BRIEF-A; Rabin et al., 2006) is a 75-item standardized self-report measure that assesses an individual's perception of their self-regulation in their everyday environment. It yields nine reliable subscale scores reflecting executive functioning (e.g. inhibit, self-monitor) and two broader indices: Metacognition and Behavioral Regulation. The Behavioral Regulation score is the measure of interest. ***B. Implicit Cognition.*** We have shown that a stronger attentional bias towards cocaine related stimuli and stronger implicit beliefs about the positive consequences of cocaine use predict worse treatment outcome during behavioral interventions (Carpenter et al., 2006, 2012). The **Drug Stroop task** has been utilized by our group in other treatment studies (Carpenter et al., 2006) and will assess the strength of an attentional bias towards cocaine stimuli. The **Implicit Relational Assessment Procedure** (Barnes-Holmes, 2008) will assess the strength of implicit beliefs about the positive and negative consequences of cocaine use. **BEHAVIORAL MECHANISM: Relapse Prevention Skills***: **Coping Strategies Scale (CSS) – Brief Version. (4 mins**)* (Litt et al., 2005) The utilization of coping skills is central to behavioral interventions for substance use. We will assess the extent to which patients report using the coping skills taught in the TES intervention. The CSS is a 23-item questionnaire (originally adapted from the Processes of Change questionnaire, Prochaska et al., 1988) that assesses coping skills such as problem solving and dealing with urges to use substances of abuse. This scale will be of primary importance to assess the extent to which the treatments differentially impact the development of coping skills. **VERBAL MECHANISM: Commitment Language***:* Language is the primary vehicle of counseling interactions and it promotes self-regulation (Hayes et al., 1986).The strength of in-session commitment language predicts treatment outcome among substance abusers over a one-year period (Amrhein et al., 2003). Patient language will be coded with Dr. Paul Amrhein's (a consultant for this proposal) system at baseline and at week 5 (the first week individuals would be randomized to either MAS-ER or PLACEBO) and relate these assessments to treatment outcome. The DARN-C coding is reliable (Amrhein et al., 2003), Dr. Amrhein's lab will code the therapy sessions; coders will be blind to patients outcomes and treatment assignments. For this set of analyses Baseline and Week 5 assessments will be used to predict treatment response (multiple comparison corrections will be used to reduce the chance of Type I errors).**]**

C14. Exploratory Analyses. A series of analyses will also be conducted to investigate the effect of each treatment condition on the key cognitive domains assessed and coping skills over time. The analysis of secondary outcomes collected over time will be based on Mixed Effect Models (MEM) for longitudinal data (Diggle et al., 2002). MEM requires no parametric distributional assumptions, provides robust inference with respect to misspecification of the covariance, and allows for the analysis of continuous, categorical and count data which may be missing for some patients either because of a missed week or due to drop-out, thus complete information for all patients is not needed. PROC NL MIXED or GLIMMIX in SAS will be used to carry out these analyses. The analyses will be used to separately test the effect of treatment condition on the magnitude of change between week 5 and week 14 for each the cognitive functioning domains and coping skill acquisition factors. Treatment condition and treatment by time interaction terms will be entered as predictors. This approach is potentially more sensitive to treatment effects since it incorporates each measurement period and effects of time. A treatment effect would be reflected in a significant main effect of either treatment or treatment by time interaction. If appropriate, baseline level of cocaine use will also be included as a covariate to test if it moderates the effect of treatment on the cognitive and behavioral outcome measures.

Future Directions: The proposed clinical trial seeks to identify key cognitive-verbal predictors of response to a behavioral intervention and test the efficacy of enhancing a behavioral treatment with amphetamine to improve treatment outcome among cocaine dependent individuals who fail to respond to the behavior therapy alone, arguably the subpopulation of patients most in need of pharmacotherapy. Identifying cognitive-verbal predictors of treatment response may help guide the refinement of behavioral treatment strategies. Further, similar to other areas of medicine, it may be that a dynamic, sequential treatment that integrates alternative intervention strategies based on patient response, will have greater efficacy than any one approach alone. If positive, the results of this trial may provide a rationale for further behavioral treatment development (Stage 1 or 2) or the investigation of this sequential treatment approach in community settings (i.e. a Stage III trial), which may set the stage for disseminating a critically important treatment strategy to the greater community of clinicians treating cocaine-dependent patients. In addition, this treatment paradigm can help stimulate further experimental research by providing a treatment platform that may help facilitate a better understanding of the neurobiological and cognitive underpinnings by which these interventions exert their effects.